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PLACENTA PERCRETA

Report of Two Cases

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PLACENTA PERCRETA is a rare but catastrophic obstetric complication. Reports of only 10 authenticated cases[1-10] have been found in the English literature; we are presenting two additional cases.

To facilitate understanding of this clinicopathologic entity, we first shall describe pertinent features of normal placentation.

Aspects of Normal Placentation

The decidua basalis is that portion of the decidua underlying the placenta, and throughout its circumference is continuous with the decidua vera; it is composed of the compact, spongy, and basal layers. The surface of the compact layer is partially replaced by a fibrinous zone that is referred to as Nitabuch's stria and which forms the boundary between fetal and maternal structures of pregnancy (Fig. 1a). Our observations, which indicate that separation of the placenta occurs beneath this plane, are confirmed by the presence of a thin layer of compact decidual tissue on the surfaces of separated placentas (Fig. 1b). The spongy layer contains dilated maternal blood vessels in its stroma as well as occasional isolated trophoblastic cells that represent *unorganized* penetration

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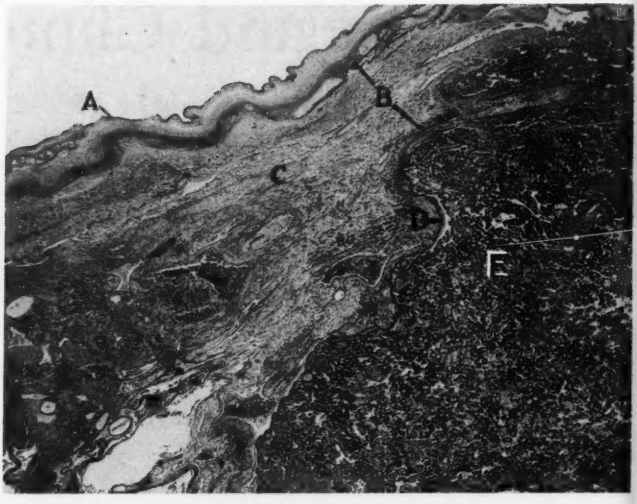
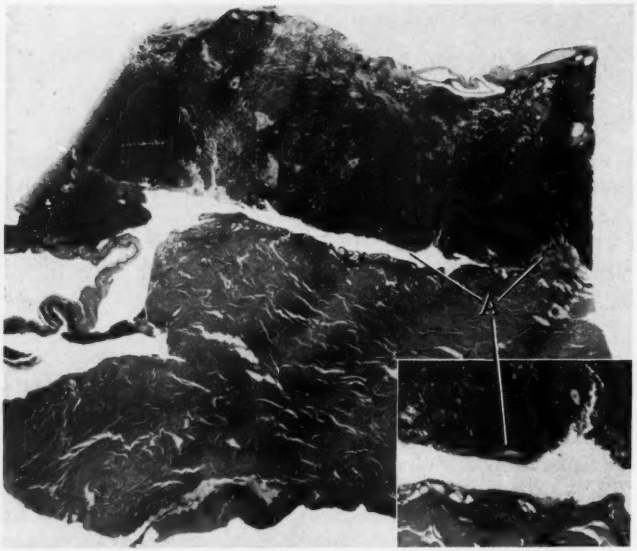
(a)





(b)

Fig. 1. (a) Normally implanted placenta. (A) amnion, (B) decidua, (C) myometrium, (D) Nitabuch's stria, and (E) chorionic villi. Hemotoxylin-eosin and methylene blue stain; X 10. (b) Celloidin section of normal placenta showing partial separation with (A) segment of Nitabuch's stria attached to placenta. Hemotoxylin-eosin stain; X 1½; insert X 5.

through the compact layer. The basal layer is composed of a single zone of proliferating cells in juxtaposition to the myometrium.

The differentiation of Rohr's stria and Nitabuch's stria is not always clear-cut because they are similar histologically although they have different origins. Rohr's stria, of *fetal* origin, is a fibrinous layer that lines the intervillous spaces; in the separated placenta this fibrinous layer is covered by syntrophoblast. Nitabuch's stria is of *maternal* origin and is part of the decidua basalis; it is thought to be structural evidence of decidual antitryptic activity in response to the stimulation of the proteolytic enzyme produced by trophoblastic cells.[11]

Placenta Percreta

Placenta percreta occurs when chorionic villi penetrate completely through the myometrium, because of an abnormal decidua, manifested by partial or complete absence of Nitabuch's stria, and an abnormal underlying myometrium caused by previous trauma.

Pathologic findings associated with placenta percreta are those so well described by Irving and Hertig[12] in their classic article reviewing the world literature on placenta accreta and include: absence of an intact decidua basalis, penetration of trophoblastic cells into the myometrium, thinning of the uterine wall beneath the placental site, degeneration of the myometrium, and chronic or acute inflammatory reaction. Conditions contributing to these pathologic changes as summarized by McKeog and D'Errico[13] include: cesarean section, dilatation and curettage, manual removal of the placenta, placenta previa, infection, neoplasm, irradiation and caustic drugs, congenital anomalies, and cornual implantation of the placenta. Meyerhardt[10] cites adenomyosis as an etiopathologic factor in placenta accreta.

Case Reports

Case 1. A 36-year-old woman, gravida X, para 0, was first examined at the Cleveland Clinic on July 15, 1957. Her history included nine spontaneous abortions, varying from 6 to 22 weeks of gestation. Dilatation and curettage (D. and C.) was required after eight of the abortions; in addition, after the ninth spontaneous abortion and D. and C., the uterus was packed with gauze because of excessive bleeding.

At the time of examination the uterus was enlarged to the size of a six weeks' pregnancy; the beginning of the last menstrual period was on June 2, 1957. Findings from the complete physical examination otherwise were normal. The hemoglobin content of the blood was 14.4 gm. per 100 ml.; hematocrit value was 41 volumes per cent; leukocyte count was 8,500 per cu. mm.; blood Wassermann test was negative, and results of urinalysis were within the normal range. A diagnosis of pregnancy in a woman who had had habitual abortions was made, and a regimen of bioflavinoids, progesterone, and mineral-vitamin capsules was prescribed.

The pregnancy progressed uneventfully to the fourth month, at which time the patient was admitted to the Cleveland Clinic Hospital (September 26, 1957) because of pain in the abdomen, nausea, vomiting, and diarrhea since the preceding evening. She had fainted twice while erect.

Physical examination revealed a patient writhing with abdominal pain and perspiring

freely. The oral temperature was 95.2 degrees F.; blood pressure was 115/80 mm. of Hg, and pulse rate was 80. The laboratory findings were: hemoglobin content of the blood, 10.4 gm. per 100 ml.; hematocrit value, 32 volumes per cent; leukocyte count, 23,000 per cu. mm., with 94 per cent neutrophils.

Positive findings were limited to the abdomen, which was soft, protuberant, and tympanitic; there were mild, generalized, muscle guarding and rebound tenderness in the right lower quadrant and in the midepigastrium. Peristalsis was active with high-pitched sounds.

The clinical impression was that the patient had severe gastroenteritis. Because of the especial importance of this pregnancy, sedation and antibiotic therapy were immediately instituted. Five hours later the temperature was 97.6 degrees F.; blood pressure was 110/80 mm. of Hg, and pulse rate was 80. The hemoglobin content of the blood was 10.4 gm. per 100 ml.; hematocrit value was 31 volumes per cent; and leukocyte count was 25,000 per cu. mm. with 94 per cent neutrophils.

The patient continued to have nausea and vomiting. She frequently passed liquid stools, cultures of which were negative for *Micrococci*, *Salmonella*, *Shigella*, and parasites; no occult blood was present. Surgical consultation was obtained and the clinical findings were confirmed, but a definite diagnosis could not be made.

Shortly thereafter, while receiving nursing care, the patient was turned on her left side and suddenly went into shock, exhibiting pallor, apprehension, and air hunger. The blood pressure dropped to 85/50 mm. of Hg; the pulse rate rose to 160; the hemoglobin content of the blood was 8 gm. per 100 ml.; the hematocrit value was 24 volumes per cent; and the leukocyte count was 18,500 per cu. mm. Fluids and blood were administered intravenously. A diagnosis of massive intraabdominal hemorrhage was made and an immediate laparotomy was performed under general anesthesia. The abdominal cavity contained approximately 3,000 ml. of both liquid and clotted blood. The uterus was enlarged to the size of that of a four-month pregnancy, and high on the posterior wall there were two perforations measuring approximately 3 cm. in diameter through which placental tissue protruded. Because of the patient's precarious condition, a rapid supracervical hysterectomy was performed. During this procedure 5 units of whole blood was given.

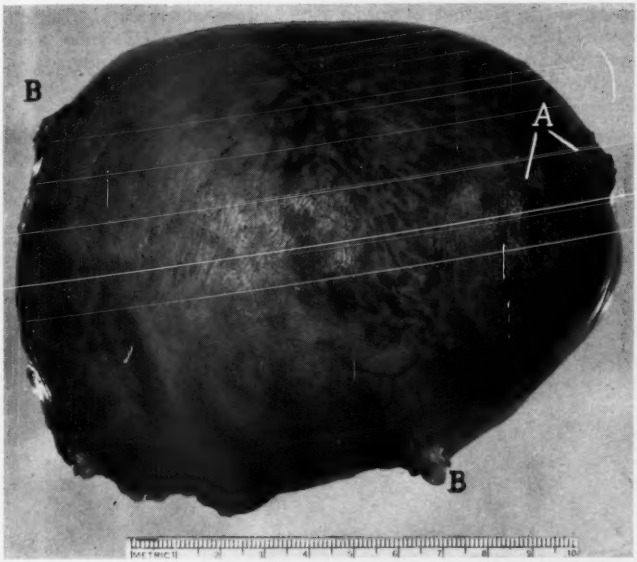
The patient had an uneventful recovery except for superficial thrombophlebitis, and she was discharged on October 9, 1957.

Pathologic findings. The gross specimen consisted of a supracervically amputated uterus with a soft globular protrusion, 5 cm. in diameter, on the posterior wall in the region of the right cornu. In the center of this protrusion two soft red masses of friable tissue measuring 2 cm. by 2 cm. issued from perforations of the myometrium (Fig. 2). Within the uterus, the amniotic cavity contained 150 ml. of fluid and a fetus measuring 10.5 cm. in length and weighing 40 gm. The placenta was implanted in the right cornu of the uterus, where the entire thickness of the myometrium had been replaced by placental tissue (Fig. 3). Elsewhere grossly the myometrium was normal.

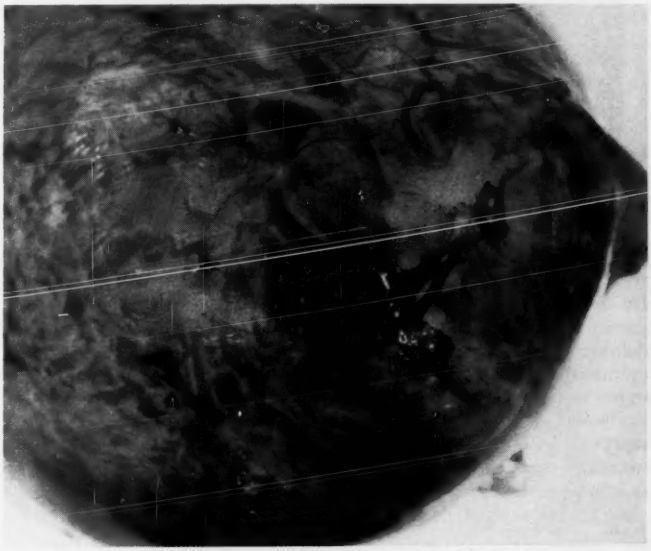
In stained sections of the placental uterine junction, chorionic villi and trophoblastic cells and masses of Langerhans cells extended directly into the myometrium; the decidua basalis was absent. Scattered individual trophoblasts were in the adjoining muscle. In sections taken at the site of perforation the myometrium was completely replaced by chorionic villi (Figs. 4 and 5). The diagnosis was placenta percreta.

Case 2. *A 36-year-old woman, the wife of a physician, gravida VI, para III was ad-

**A report of this case in regard to the use of the antigravity suit is to be published.*



(a)



(b)

Fig. 2. (a) Photograph of the uterus showing bulging of the right cornu with two areas of perforation (A); round ligaments (B). (b) Enlarged photograph of area of perforation.

mitted to the hospital* on the afternoon of April 3, 1955, because of irregular uterine contractions and bleeding. Her history included two previous vaginal deliveries; the second delivery had necessitated extensive cervical and perineal repair. The third child had been delivered by an elective transverse laparotrachelotomy in order to preserve the cervix and the perineum. Since then the patient had had two spontaneous early abortions, each of which required dilatation and curettage and was followed by excessive bleeding that was controlled by intrauterine packing and transfusions. During the first five months of the sixth pregnancy there had been almost continuous spotting without cramps. The membranes spontaneously ruptured at the twenty-fourth week of pregnancy and 48 hours later she had slight spotting with irregular uterine contractions.

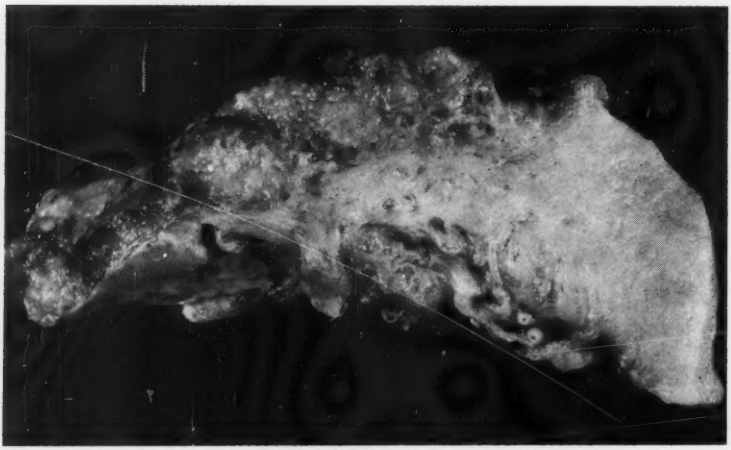


Fig. 3. Gross section of the uterine wall showing progressive placental invasion of myometrium with perforation at the extreme left.

On the evening of admission there was moderate vaginal hemorrhage followed by regular progressive uterine contractions and a decrease in the amount of bleeding. The blood pressure was 134/72 mm. of Hg. No fetal heart tones were audible. Labor progressed slowly and at 3:45 a.m. on April 4, under spinal anesthesia, a stillborn fetus was delivered, and immediately thereafter severe bleeding occurred. Loss of blood was estimated to be 1,500 ml. Prompt manual exploration of the uterine cavity revealed the upper half of the placenta to be completely detached from the anterior uterine wall, but the lower half of the placenta, which extended downward to the external cervical os, was tightly adherent to the uterine wall. The separated portion of the placenta was removed manually, and gentle attempts were made to separate the lower section. It was apparent that this was impossible, and a diagnosis of placenta accreta was made. Since the patient was showing signs of shock, the uterus was tightly filled with 10 yards of intrauterine

This patient was delivered at Saint Luke's Hospital in Cleveland, Ohio. We wish to acknowledge the skill and assistance of Dr. Donald M. Glover, Chief of Surgery, Dr. B. B. Sankey, Chief of Anesthesiology, and their staffs, especially the blood bank personnel.

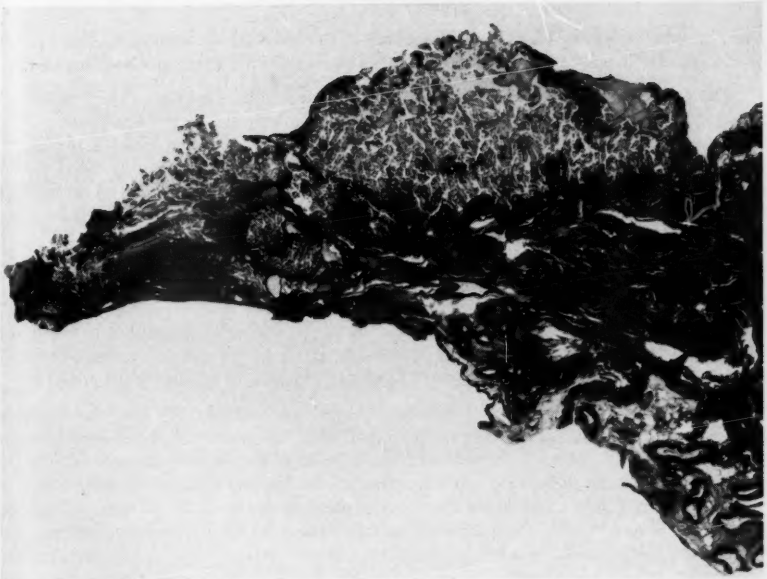


Fig. 4. Celloidin section of uterine wall shown in Fig. 3, showing replacement of myometrium by chorionic villi with site of perforation at extreme left. Hemotoxylin-eosin and methylene blue stain; X 1.5.

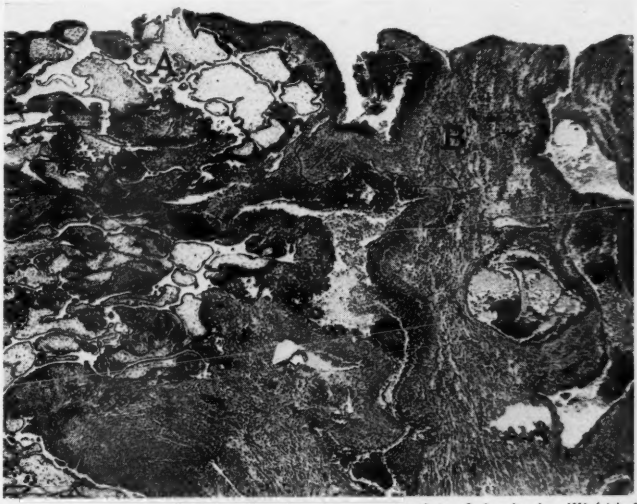


Fig. 5. Section near the site of perforation showing penetration of chorionic villi (A) deep into the myometrium (B); decidua basalis is absent. Hematoxylin-eosin and methylene blue stain; X 14.

packing, and she was given fluids and one unit of whole blood intravenously. The patient rallied quickly from the state of shock, and an emergency hysterectomy was begun.

The abdominal cavity was entered through a lower midline incision. The fundus was found to be well contracted; however, on the dilated anterior surface of the lower uterine segment there was a roughly circular area, about 20 cm. in diameter, which appeared to be similar to the fetal surface of the placenta with large, dilated, interlacing blood vessels coursing beneath a thin membrane. The intrauterine pack was removed, and the patient again went into a state of shock. The bladder reflection could not be mobilized from what was presumed to be the anterior uterine wall. The fascial plane containing the large dilated veins was penetrated, disclosing placental tissue immediately beneath it. The placenta had completely invaded and replaced the myometrium of the lower uterine segment. The uterine arteries were ligated and a supracervical hysterectomy was carried out. There was troublesome bleeding from the placenta, which remained beneath the bladder. The bleeding was partially controlled by figure-of-eight ligatures, Oxycel* gauze, and the pressure of the advanced bladder reflection over this oozing stump.

Because of the patient's condition rapid closure was carried out. Since the delivery, four hours previously, and the emergency laparotomy the patient had received 11 units of blood and 3,000 ml. of 5 per cent dextrose in water. The blood pressure was 110/50 mm. of Hg, and the pulse rate was 130. Ten hours after the delivery, despite the continued use of multiple transfusions, the blood pressure dropped to 70/60 mm. of Hg, and the pulse rate rose to 140. The abdomen became distended and tympanitic, and respiratory distress developed. It was obvious that massive intraabdominal hemorrhage had occurred.

Eleven hours after delivery the patient was moved to the operating room and under cyclopropane anesthesia a vaginal pack was inserted and the abdomen was reopened. An estimated 3,500 ml. of clotted and liquid blood was removed from the peritoneal cavity, 1,000 ml. of which was filtered and retransfused. At the time, the patient was receiving transfusions of blood or fluids into four veins simultaneously. Bleeding was chiefly from a spongelike mass of placental tissue beneath the bladder. There was bleeding from both broad ligaments and from the stumps of the round ligaments and tubes; these were re-ligated. More figure-of-eight sutures were placed in the remaining placental tissue, and for a while all bleeding seemed to be controlled. However, within a few minutes, as the patient was receiving approximately her thirtieth transfusion, oozing developed from many sources and blood was found in the urine. The right hypogastric artery was ligated without effect and temporary ligatures of the common iliacs had no effect. The bleeding was from the peritoneal surfaces as much as from the area about the retained placenta. In addition to citrated blood, the patient received 1,000 ml. of whole blood by silicone syringes, 3 units of fibrinogen, 1 unit of serum albumin, Cortef** (intravenous), and 20 ml. of calcium gluconate. Blood was simultaneously administered intraarterially and intravenously several times during the long operation to keep systolic pressure above the level of shock.

After six hours of anesthesia and attempts to control bleeding, the prognosis appeared hopeless. Therefore, since massive packs with pressure had been the only means capable of somewhat controlling the bleeding, nine large abdominal tapes (each 8 in. by 36 in.) were placed in the abdomen, the incision was partially closed, and the patient was returned to her bed. Sand bags were placed on the abdomen; the legs were wrapped with elastic bandages; and the foot of the bed was elevated on shock blocks. Within 18½ hours

*Parke, Davis & Company, Detroit, Michigan.
**The Upjohn Company, Kalamazoo, Michigan.

of delivery, the patient had received 55 units of blood (including two units recovered from the peritoneal cavity, and two units of fresh blood), and approximately 10,000 ml. of other fluids. While two additional units of blood were being transfused, the blood pressure was 86/62 mm. of Hg and the pulse rate was 144. At this juncture the antigravity ("G") suit was applied and inflated to 20 mm. of Hg. Within five minutes the blood pressure rose to 104/72 mm. of Hg.

The rate of transfusion was slowed and the blood pressure gradually rose to 114/80 mm. of Hg, while the pulse rate increased to 160. Within 24 hours of delivery the patient had received 58 pints of blood,* the blood pressure had become stabilized, and the pulse rate had begun to decrease. The 24-hour output of urine was 415 ml.

Thirty-six and one-half hours after delivery, and after 18 hours in the G-suit (which was deflated and removed after a total of 24 hours), the blood pressure was 130/78 mm. of Hg, and the pulse rate was 130. Seventy-two hours after operation, the abdomen was reopened, a quantity of clot was evacuated, and the abdominal and vaginal packs were removed. There was no further bleeding, and the vital signs remained stable. Subsequently there were ileus, atelectasis, and fever. In the fifth week, a left subphrenic abscess had to be drained abdominally. The patient was discharged on the fifty-fourth hospital day. From then on convalescence was uneventful except for a mild episode of hepatitis that developed on the one hundred and twenty-ninth day.

Discussion

It is impossible to make an antepartum diagnosis of placenta percreta that does *not* penetrate into the abdominal cavity (Case 2). When symptoms of intra-abdominal hemorrhage occur during the second or third trimester of pregnancy (Case 1) placenta percreta as well as spontaneous rupture of the uterus should be considered in the differential diagnosis. History of repeated intrauterine insult, absence of uterine contractions, prior to onset of symptoms, and gradually increasing symptoms of intraabdominal hemorrhage suggest placenta percreta rather than spontaneous rupture of the uterus. Upon diagnosis of intraabdominal hemorrhage, treatment for shock and a laparotomy become mandatory. When placenta percreta is encountered, hysterectomy, preferably total, usually is indicated. Careful examination of the excised uterus may be necessary to distinguish between placenta percreta and spontaneous rupture of the uterus with herniation of the placenta.

Severe loss of blood may require massive replacement transfusions. Uncitrated fresh whole blood, calcium gluconate and fibrinogen may be administered to aid in maintaining the blood-clotting mechanism. In spite of these heroic measures bleeding from serous surfaces may at times demand measures of tamponade, such as intraabdominal packs and use of the antigravity suit. This seems to be a means of "buying time" until the patient's own clotting mechanisms and normal capillary permeability can function.

We believe that placenta percreta results from deficiencies of the endometrium and myometrium, caused by previous (and often repeated) insults, such as cesarean section, dilatation and curettage, and manual removal of placenta, which permit invasion of the entire thickness of the uterine wall by

**This 29,000 ml. of blood represents, to our knowledge, the largest amount of blood transfused in a patient during a 24-hour period.*

trophoblastic elements. Placenta percreta, by definition, has perforation as a characteristic feature, and perforation can occur into the abdominal cavity (Case 1), beneath the bladder reflection (Case 2), or between the sheaths of the broad ligaments.

The basic process of invasion of the myometrium by trophoblastic cells may be compared to the condition present in tubal pregnancy, leading to invasion and perforation of the tubal wall, wherein the mucosa and muscularis of the tube are structurally not suitable for placental implantation. In either condition it is the character of the tissue underlying the area of nidation which determines the extent of the penetration of the chorionic villi, and not, as some have suggested,[14] overaggressiveness of the trophoblast.

When deficiency of the endometrium alone exists, placenta accreta may develop; when the deficiency extends into the superficial layers of the myometrium, placenta increta is likely to develop (Figs. 2 and 3); when defects extend deeply into the myometrium, placenta percreta becomes a distinct probability.

Conclusions

1. Placenta percreta is a serious obstetric complication. It results when trophoblastic cells and chorionic villi traverse the uterine wall, culminating in perforation of the uterus. Causative are various pathologic changes that are due to previous, repeated, severe intrauterine insults leading to the formation of an abnormal endometrium and an abnormal underlying myometrium. A manifestation of this deficiency may be partial or total absence of Nitabuch's stria when implantation takes place. If Nitabuch's stria is absent, an *organized* invasion by the trophoblast of the underlying uterine wall may occur.

2. Placenta percreta may be suspected clinically in the second or third trimester of a pregnant woman who, in addition to a typical history of repeated intrauterine manipulation, exhibits signs of gradually increasing intraabdominal bleeding. Placenta percreta may be difficult to differentiate from spontaneous rupture of the uterus.

3. Treatment for shock and a hysterectomy in most instances are the only therapy; together they constitute a lifesaving procedure. In administering repeated transfusions, precautions to prevent incoagulability of the blood and abnormality of capillary permeability must be considered.

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MANAGEMENT OF BLEEDING FROM ESOPHAGEAL VARICES

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THE goal of treatment of portal hypertension and bleeding esophageal varices is the control of hemorrhage and the prevention of its recurrence. Publications have dealt chiefly with the selection of cases, operative mortality, and technical matters of interest to those entrusted with definitive treatment, but have not elaborated upon two important points: (1) the practical measures that may be taken by the general practitioner who sees the patient first, and (2) the effectiveness of the various operative procedures in preventing recurrent bleeding.

This discussion is presented in the belief that it is the *initial* treatment of the cirrhotic patient with bleeding varices that largely determines whether or not he will survive a bleeding episode and recover to the extent that surgical measures may be safely undertaken to prevent recurrent hemorrhage. A program of management is outlined which may be carried out rapidly, is adaptable to the community hospital, and offers the patient a maximum opportunity for survival.

The Problem in the Bleeding Cirrhotic Patient

The high mortality associated with gastrointestinal bleeding in cirrhotic patients is well known. Approximately one quarter to one half of any group of cirrhotic patients will bleed each year, and the mortality due to hemorrhage is from 25 to 75 per cent. Half of those who survive will bleed again within the year with a mortality of 50 per cent.[1,2] The reserve of the damaged liver is easily compromised by shock, anoxia, severe infection, or the presence of a large amount of blood in the intestinal tract. The essentials of emergency treatment are *rapid control of bleeding*, *protection against infection*, *purgation of the bowel*, *restriction of sodium*, and *intravenous administration of dextrose*.

Emergency major surgical operations are poorly tolerated by cirrhotic patients, as shown by an average emergency mortality of more than 50 per cent.[3,4] Balloon tamponade, on the other hand, will readily control bleeding in from 80 to 90 per cent of patients.[5] Bleeding not readily controlled by tamponade requires the least traumatic surgery necessary to control it, through an approach that will permit appropriate treatment of bleeding lesions other than the varices. Transthoracic suture and mediastinal packing are not suitable therefore, and gastric transection, esophagogastrectomy, or emergency shunt seldom are necessary.

Noncirrhotic patients with extrahepatic portal block and bleeding varices will tolerate emergency major surgery well, but tamponade and further evaluation of the patient are safer when little is known about the patient.

Children with unsuspected postnecrotic cirrhosis and bleeding varices may not survive surgery that is undertaken in the mistaken belief that because they are children they must have extrahepatic portal block. The diagnosis of post-

hepatitic cirrhosis in children is being made with increasing frequency. Reliance upon liver function studies or gross appearance of the liver may be misleading; biopsy of the liver is the only certain way of determining the presence or absence of cirrhosis.

Emergency Control of Bleeding

Balloon tamponade, using the recently redesigned triple-lumen Sengstaken-Blakemore tube*, offers the safest, most rapid and effective means of controlling

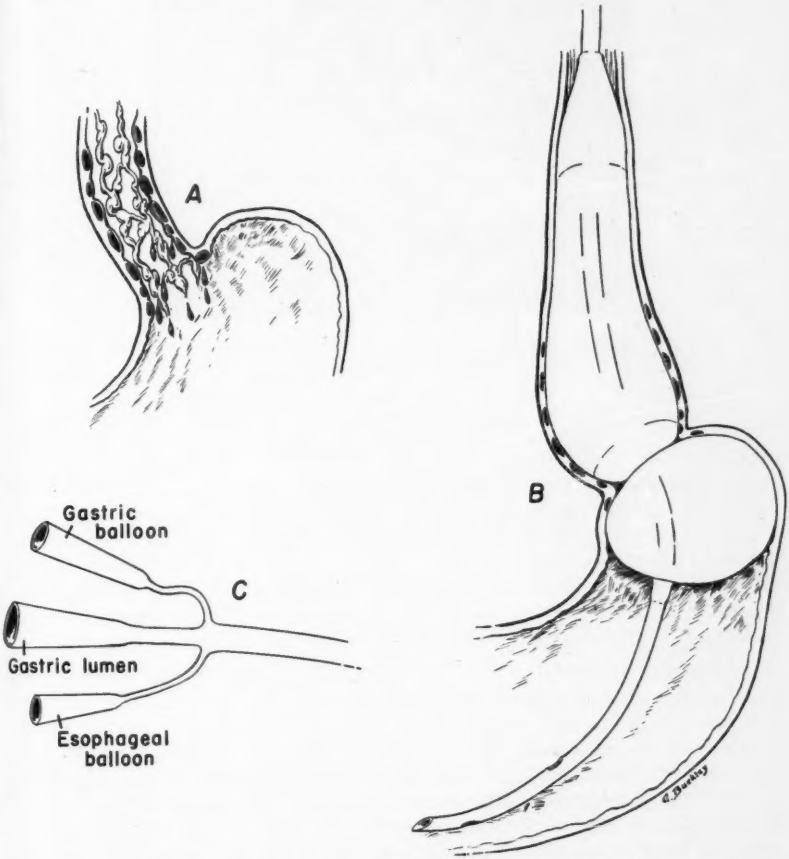

Fig. 1. Diagram demonstrates the principle of *lateral* tamponade of esophageal varices with the Sengstaken-Blakemore tube. *A*, bleeding esophageal varices; *B*, esophageal and gastric balloons and gastric tube in place; *C*, proximal aspect of tube.

*Manufactured by the Davol Rubber Company, Providence, Rhode Island.

esophageal bleeding and of making the patient safely *transportable* (Fig. 1). The principle of its use is *lateral* tamponade of varices by means of a triple-lumen tube with a long esophageal balloon reinforced at top and bottom to prevent herniation into the pharynx or the stomach, and a distal gastric balloon that serves chiefly to prevent regurgitation of the tube, and secondarily to tamponade varices in the gastric fundus when light traction is applied to the tube (Fig. 2).

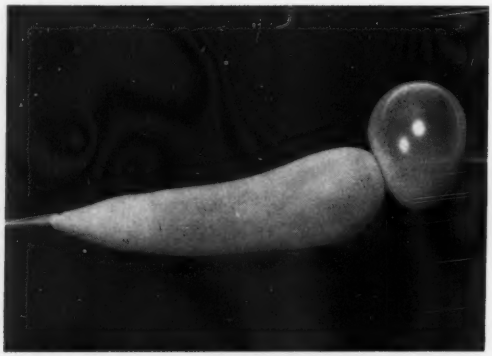

Fig. 2. Photograph of the inflated Sengstaken-Blakemore tube. Note the eccentricity of the gastric balloon for positioning it in the gastric fundus.

The eccentric doughnut shape apparent in Figure 1 is for the latter purpose. The central large lumen is for gastric aspiration and feeding. Unlike the single large gastric balloon advocated by some, which depends upon strong traction to occlude all venous collateral vessels at the esophagogastric junction, the Sengstaken-Blakemore tube may be left in place for weeks, if necessary, to prevent further bleeding while the patient is being prepared for a definitive operation. When a significant amount of traction is required to control bleeding, it must be released after 24 hours to prevent mucosal erosion and necrosis. If new bleeding occurs at this point, other measures discussed below are in order.

In practice it is useful to have readily available a tray bearing a balloon, an atomizer containing 5 per cent tetracaine (Pontocaine) hydrochloride or 10 per cent cocaine, a large-stemmed 50-cc. syringe, two rubber-shod clamps, a glass Y tube, and rubber tubing for attachment to any standard sphygmomanometer (Fig. 3). The patient should be kept under sedation with liberal doses of meperidine (Demerol) hydrochloride unless he is comatose. The nares and pharynx are sprayed with the topical anesthetic solution; the balloons are deflated; and the tube, lubricated with a water-soluble lubricant, is passed through the nose into the stomach while the patient sips water—the numbers on the tube being kept toward the patient's right side to insure that the eccentric portion of the gastric balloon will protrude toward the fundus of the stomach. The gastric balloon is then inflated with 150 cc. of air and the tube is withdrawn until the gastric

balloon engages at the esophagogastric junction. Then the tube is taped to the plastic sponge block in order to prevent pressure necrosis of the nasal ala. The esophageal balloon tube is attached to the Y tube, the other limb being attached to the sphygmomanometer. A rubber hand bulb is attached to the remaining end of the Y tube and the esophageal balloon is inflated to an initial pressure of 45 mm. of Hg, and the tubes of both esophageal and gastric balloons are clamped with the rubber-shod clamps to prevent air from leaking from the system (Fig. 3). The stomach tube is then thoroughly irrigated and aspirated with

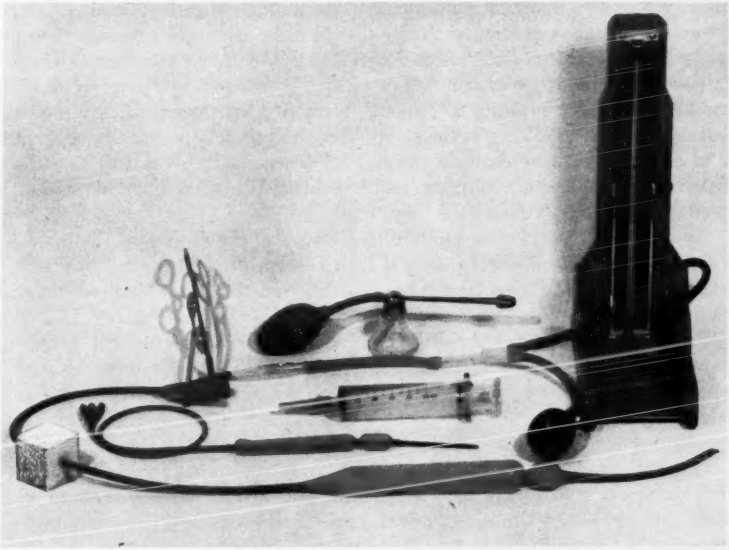

Fig. 3. Photograph of the standard equipment used in passing the Sengstaken-Blakemore tube. Note the small pediatric-sized tube.

copious amounts of tap water until the return is clear; then the gastric lumen is put on continuous intestinal suction. If the return is still clear one-half hour later, suction is discontinued and castor oil (60 cc.) and neomycin (1 gm.) are instilled into the tube for the purpose of purging the intestinal tract of blood which may be converted by the intestinal organisms into ammonium compounds which may produce coma. An hour later suction is resumed and continued except during instillation of purgative and neomycin every 6 hours (for a total of three doses), and during irrigation of the tube every hour. If an esophageal-balloon pressure of 45 mm. of Hg is poorly tolerated by the patient, the pressure may be reduced, preferably by 5-mm. stages, to the lowest pressure that will control bleeding.

Intravenous hydration and restoration of blood volume are then effected, with special care to administer as many calories as possible in the form of carbohydrates. Systemic antibiotic agents such as procaine penicillin (300,000 units)

and streptomycin (0.5 gm.) every 12 hours, or one of the tetracycline drugs (500 mg.) every eight hours, should be administered parenterally to supplement the effect of neomycin in the bowel and to control possible respiratory infection to which these patients are subject during intubation. Vitamin K_1 (50 mg. intravenously), ascorbic acid (1,000 mg.), vitamin B_{12} (50 μg.), and multiple vitamins rich in vitamin-B complex should be given after blood has been withdrawn for base line studies of liver function.

Retching and substernal discomfort caused by the tube usually are alleviated by instructing the patient to hyperventilate for a minute, by elevating the head of the bed of the conscious patient, by keeping the stomach empty, and by adequate sedation with meperidine hydrochloride. Because the inflated esophageal balloon completely obstructs the esophagus, salivary secretions cannot be swallowed; therefore, the conscious patient is instructed to expectorate all secretions. Comatose patients require frequent pharyngeal suctioning. It is amazing how well the tube is tolerated after the first few hours. Periodic checking of the amount of tension on the tube is necessary in order to take up slack as the diaphragmatic crura of the esophageal hiatus relax. Esophageal-balloon pressure should be checked every half hour.

On the third day of tamponade the pressure in the esophageal balloon may be reduced to 25 mm. of Hg and, if no bleeding occurs, the balloon may be deflated and the tube may be removed on the fourth day. This time interval is based roughly upon the "lag" period for healing of most soft tissues. If a definitive operation to reduce portal hypertension is to be performed in another hospital, the balloon should be left in place while the patient is being transported. After an episode of bleeding, most cirrhotic patients require a minimal period of three weeks for complete recovery, and consideration of a major surgical procedure.

The appearance of stupor, bizarre behavior, a flapping tremor of the hands when the arms and fingers are extended, along with a marked fetor hepaticus usually herald coma. These changes may be due in part to ammonium intoxication, which is discussed below.

Failure of Balloon Tamponade

If, within a half hour after passage of the tube, irrigation of the stomach still returns red blood, it is obvious that bleeding has not been controlled. From 10 to 20 per cent of cirrhotic patients bleed from gastric varices, peptic ulcers, or other lesions out of reach of balloons.[6] Such patients require immediate surgical intervention for control of hemorrhage. The most limited operation that will control bleeding is indicated if the patient has serious hepatic impairment. Endotracheal cyclopropane is the anesthetic agent of choice since it induces anesthesia in the patient rapidly, provides adequate relaxation, and permits the use of a high concentration of oxygen. Spinal analgesia may be dangerous if coagulation factors are abnormal, as they so frequently are in these patients. Transabdominal suture of gastric varices beyond the reach of the balloon, through a simple gastrotomy wound in the anterior wall of the stomach, can be

performed rapidly and with the least risk. All time-consuming and nonessential procedures must be avoided; these include measurement of portal pressure and suture of esophageal varices that can be reached by the balloon. Considerable judgment is required in deciding whether or not to proceed with gastric resection for treatment of a bleeding duodenal or gastric ulcer in a patient with obvious impairment of the liver. Gastric resection is usually mandatory for hemorrhagic gastritis, frequently is necessary for bleeding duodenal ulcer, but suture usually suffices for bleeding gastric ulcer.

Ammonium Intoxication and Stupor

It is now apparent that an abnormally increased concentration of ammonium ions in the blood will produce symptoms progressing from stupor to bizarre behavior, coma, and death. The source of the ammonium in most of these patients appears to be from bacterial decomposition of blood within the intestinal tract. The source in the nonbleeding cirrhotic patient may be his dietary protein. The increase in peripheral blood ammonium is due to inability of the damaged liver to convert ammonium to urea at a normal rate, and to direct passage of portal blood into the peripheral circulation through naturally occurring portasystemic shunts in the esophageal and other collateral systems. The liver of the noncirrhotic patient with gastrointestinal bleeding is able to convert ammonium to urea rapidly, and no significant shunts exist. The noncirrhotic patient who has a large surgically created portasystemic shunt and who takes a high-protein diet may have high concentrations of ammonium in the peripheral blood because the liver is bypassed. Prolonged oral administration of neomycin has proved effective in protecting most patients from coma, thereby permitting ingestion of the all-important high-protein diet. The actual incidence of chronic ammonium poisoning in patients who have surgical shunts is not determined, but clinically is less than 5 per cent.

Two measures have proved effective in rapidly lowering the concentration of ammonium in the blood and, if coma is predominantly due to that condition, in dramatically reversing coma within hours. The first measure aims at reducing the numbers of intestinal organisms that produce the ammonium, and consists of the administration of from 1 to 2 gm. of neomycin by mouth or by nasogastric tube, every six hours, along with the use of purgatives to rid the bowel of blood. The second measure consists of the intravenous administration of 25 gm. of arginine hydrochloride with 50 gm. of dextrose in 500 ml. of water, or of one of the newer commercial preparations of the glutamic acid salt of arginine every six hours. Although no harmful effects of these preparations are known, other than acidosis from arginine hydrochloride and alkalosis and sodium overload from sodium glutamate, they are best reserved for the appearance of neurologic changes or the demonstration of elevated concentrations of ammonium in the blood.

One of the earliest signs of impending coma may be a flapping tremor of the hands when the arms and fingers are extended forcibly by the patient. This sign is an indication for starting arginine treatment and is of greater clinical significance than is fetor hepaticus.

Prevention of Recurrent Bleeding

During the past fifty years numerous operations have been devised to treat portal hypertension and its complications. Omentopexy and portacaval shunts were designed to increase portal collateral flow. Splenectomy, ligation of the splenic and of the hepatic artery, devascularization of the stomach, and gastric transection were purported to reduce flow into the portal bed or into the varices. Transthoracic and transabdominal suture of varices and esophagogastric resection were aimed at attacking the varices directly.

To evaluate the results of the various operations in preventing recurrent bleeding, the literature was reviewed and all reports giving incidence of recurrent bleeding were compiled. These data are summarized in Tables 1 and 2.

Table 1. — *Treatment of intrahepatic block for portal hypertension (Data from a review of the literature)*

Operation	Total number of patients	Operative mortality		Cause of Death				Recurrent hemorrhage	
				Hemorrhage		Hepatic failure			
		Number of patients	Per cent of total	Number of patients	Per cent of total	Number of patients	Per cent of total	Number of patients	Per cent of total
Portacaval shunt	556	76	13	5	1	23	5	20	4
Splenectomy	136	52	38	9	10	16	19	33	48
Splenorenal shunt	107	18	16	9	10	20	22	33	37
Hepatic artery ligation	40	7	18	0	—	8	24	9	23
Suture	28	8	28	0	—	11	39	9	32
Esophagogastric resection	11	4	36	1	14	1	14	1	14
Splenic artery ligation	8	0	—	1	12	0	—	1	12
Devascularization	7	3	43	0	—	0	—	1	25
Mediastinal packing	6	0	—	2	33	0	—	3	50
Makeshift	4	0	—	1	25	0	—	3	75
Vagotomy	2	0	—	0	—	0	—	1	50

These are gross data with periods of follow-up ranging from a few months to 10 years, the longer periods being follow-ups of shunting operations. The data for several operations are too few to justify comparative analysis, and they indicate the paucity of follow-up reports of these procedures, usually because they have been abandoned.

It is clear that the portacaval shunt offers the best protection against further bleeding. It is interesting and significant that the most effective operation is that which permanently reduces portal pressure. The reasons for this would appear to be that prevention of *surge pressure*, as occurs with coughing, straining, or any

maneuver that increases intraabdominal pressure, is best accomplished by a large portal shunt at the confluence of the portal radicles emptying directly into the low-pressure vena cava[7]. Pressure studies have shown that only transient reduction in pressure results from ligation of the hepatic or the splenic artery, or from splenectomy.[8] The splenorenal shunt is smaller, more subject to occlusion, and less effective than is the portacaval shunt. The superiority of the portacaval shunt probably is due to the fact that the flow through such a shunt is proportional to the fourth power of the radius of the shunt. The average splenorenal shunt is 10 mm. in diameter; whereas, the average portacaval shunt is 20 mm. or more in diameter.

Table 2. — *Treatment of extrahepatic block for portal hypertension (Data from a review of the literature)*

Operation	Total number of patients	Operative mortality		Recurrent hemorrhage		Late fatal hemorrhage	
		Number of patients	Per cent of total	Number of patients	Per cent of total	Number of patients	Per cent of total
Splenectomy	233	18	8	154	72	18	8
Splenorenal shunt	121	5	4	33	27	5	4
Makeshift	25	1	4	13	52	3	13
Suture	19	0	—	9	47	0	—
Esophagogastric resection	8	0	—	5	62	1	13
Devascularization	6	0	—	6	100	0	—
Mediastinal packing	4	0	—	3	75	0	—
Portacaval shunt	1	0	—	0	—	0	—

For patients with extrahepatic portal block, the splenorenal shunt offers the best hope for prevention of bleeding, and for this reason splenectomy should not be performed when esophageal varices are present unless the surgeon is prepared to proceed with a splenorenal shunt. When no shunt is possible because of previous splenectomy, or because the splenic vein is thrombosed or is shown by splenoportography to be unsuitable for anastomosis, suture of varices and splenectomy offer a retrenchment short of esophagogastric resection. An exception to this is the child with a small or anomalous splenic vein; transthoracic suture of varices alone should be performed and the spleen left intact until it is clear that growth has not improved the size or the quality of the splenic vein for the purposes of anastomosis. Premature splenectomy for thrombopenia and varices usually is not justified unless a splenorenal shunt can be effected simultaneously. Esophagogastric resection usually has not been performed except as a last resort, because of the mortality and morbidity attendant upon the operation, the postoperative nutritional problems, and because most of the patients with extrahepatic portal block are children.

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PULMONARY COMPLICATIONS OF OPEN-HEART OPERATIONS: THEIR PATHOGENESIS AND AVOIDANCE

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PULMONARY complications, acidosis, and overoxygenation are three stumbling blocks to the success of open-heart operations. In one previous report[1] the problem of acidosis, its recognition, avoidance, and therapy, was discussed. In another report[2] the use of the Clark polarograph to avoid overoxygenation of blood in oxygenators was described. In this report, we shall present the thesis that temporary overloading of the pulmonary circulation with blood is the most important single factor in the initiation of capillary damage that marks the beginning of severe pulmonary complications after open-heart operations.

Methods

During the open-heart operation the patient's circulation was maintained by one of four types of pump oxygenators previously described: disposable membrane,[3] Melrose,[4] Björk,[5] Kay and Cross.[6] In many patients the heart was stopped with potassium citrate according to Melrose's technic.[7,8] During the usual postoperative care,[9] chest roentgenograms were made about three hours postoperatively, that night, and during the following days if necessary. If indicated, respiration was aided with positive pressure, during inspiration only, providing a mixture of air and oxygen or pure oxygen with a Bennett Respirator.* This was done via a cuffed tracheotomy tube when the need for more than several hours of respiratory assistance was anticipated.

Pathogenic Factors in Pulmonary Complications

1. *Pre-existing pulmonary vascular disease*, often present with long-standing pulmonary hypertension, seems to predispose to the occurrence of pulmonary

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**Bennett Respirator, manufactured by V. Ray Bennett & Associates, Inc., 320 South Robertson Boulevard, Los Angeles 48, California.*

complications after open-heart surgery. In the last 50 consecutive patients treated with the heart-lung machine at the Cleveland Clinic Hospital, some degree of pulmonary difficulty occurred 11 times. Of those 50 patients, 11 had pulmonary hypertension and in four of them pulmonary complications occurred.

2. *Oxygen intoxication of the alveolar and capillary cells*, from the undiluted oxygen administered by the anesthetist, has been thought possible to occur during the period of total bypass when the lungs are not perfused with blood. Exsiccation of the lungs may occur when they are continuously ventilated with dry gas during the period of total bypass, because no blood goes through them to keep them wet. Kirklin[10,11] and Patrick[12] have adopted the practice of keeping the lungs gently inflated with a mixture composed 50 per cent of helium and 50 per cent of oxygen to minimize the possibility of oxygen intoxication of pulmonary tissue. We have followed their example. The lungs should be kept gently inflated but still, to avoid the drying effect of a "breeze" of gases.

3. *Small children are especially susceptible to pulmonary complications.* One reason is that tiny bronchioles are more easily plugged with mucus or debris. Tracheotomy should be considered, but not done without good indication. The ease with which tracheotomy tubes in infants become mechanically obstructed by malposition or mucus certainly makes them a mixed blessing. Postponement of open-heart operations until the child has reached the age of two years is recommended whenever possible.

4. *Use of too much fluid.* Excessive amounts of mineral solution are present in some types of commercial blood-collecting bottles. Too much electrolyte or dextrose solution sometimes is given to keep the venous infusion flowing. In order to prevent an undesirable decrease in colloid osmotic pressure, Kirklin[10] and Patrick[12] compensate with albumin for all water used. We restrict the infusion of water and electrolyte solutions to small amounts.

5. *Air embolism* to the lungs, originating from the right heart, can easily occur. We have on occasion observed air bubbles emerge from puncture holes in the pulmonary artery following postcorrection measurement of pressure in that vessel. It probably is not so innocuous as many have thought. For example, the biologic lung* is quickly destroyed as an oxygenator because of undue resistance when small amounts of air are permitted to enter the pulmonary artery.[13] Lillehei[13] saw that small amounts of air injected into the pulmonary circulation of dogs resulted in large increases in pressure in the pulmonary artery, lasting about a half hour. South African investigators[14] have produced pulmonary arteriosclerosis in rabbits by repeated intravenous injections of small amounts of air. It may be recalled that slush (a mixture of air bubbles and blood), though it does not increase the resistance when flowing, causes a high resistance when the flow is interrupted.[15] The forces necessary to get slush moving again through the capillary bed may be greater than those available. A clamp on the pulmonary artery while the right heart is open, avoids this complication.

**The dog lung used as an oxygenator.*

6. *Temporary overloading of the pulmonary circulation with blood* seems to us to be the most important single factor. Evidence will be presented which suggests that such overloading, even for short periods of time, may initiate capillary damage with various degrees of extravasation of blood. In the postoperative hours and days the extent of these extravasations will increase by exudation and edema until they seriously interfere with gaseous interchange. Anoxia may then dictate the use of undiluted oxygen which, over prolonged periods of time, tends to add injury to insult.

Four Circumstances That Lead to Overloading of the Pulmonary Circulation

1. *Forward overfilling of the pulmonary vascular bed.* (a) During partial bypass (i.e., before the venae cavae are occluded), sudden overloading of the circulation with blood leads to increased pressure in the pulmonary arteries (Fig. 1A). This cannot occur during the period of total bypass when the venae cavae are tied off and the heart is open. (b) During total bypass, when the venae cavae are tied off but while the right side of the heart is closed, coronary sinus blood flows into the right atrium, and the pressure may build up so that blood is propelled through the right ventricle into the pulmonary artery (Fig. 1B). This becomes critical if "extravagant" coronary blood flow occurs when the occluding clamp is removed from the root of the aorta after potassium citrate arrest or after anoxia of the myocardium. The coronary blood flow may then amount to 50 per cent of the total circulation.[16] It rarely will lead to damage unless pulmonary outflow (as in circumstance 3 below) is impeded and/or unless the heart is arrested so that it cannot pump away the coronary return.

2. *Filling of the pulmonary vascular bed through collateral vessels.* (a) Patent ductus (Fig. 2A). (b) Increased bronchial arteries as in patients with tetralogy of Fallot (Fig. 2B). The occurrence of left heart overfilling first became apparent to us in open-heart operations for tetralogy of Fallot in which elective cardiac arrest was employed. Blood from the bronchial vessels to the left heart spilled through the septal defect until it was closed. On occasion the heartbeat would then return spontaneously because the left heart pressure had reached a level sufficient to flush the coronary circulation and to remove the potassium citrate mixture. Muller, Littlefield, and Dammann[15] have given convincing experimental proof of the importance of collateral circulation. They first provoked the development of collateral vessels by tying off one pulmonary artery; at a later date, during extracorporeal maintenance of the circulation, they clamped both the main pulmonary artery and the root of the aorta, and within minutes the pretreated lung was engorged with blood. Among our last 50 open-cardiotomy patients there were 10 patients each of whom had tetralogy of Fallot, and in two of them pulmonary complications developed.

3. *Retrograde overfilling of the pulmonary vascular bed: excess blood in pulmonary veins caused by impeded venous outflow or by backflow.* (a) Mechanical obstruction of pulmonary veins, or of a single pulmonary vein may occur following surgical attempts to correct transposition of the great vessels or following correction of

atrial septal defects with associated anomalous pulmonary venous drainage (Fig. 3A). (b) Obstruction of the mitral ostium in mitral stenosis, regurgitation of blood in mitral insufficiency or in mitral and aortic insufficiency will cause backflow into the pulmonary veins (Fig. 3B). Aortic regurgitation will not occur when the patient is maintained on the heart-lung machine if the aorta is clamped for arrest, but will commence upon removal of the clamp from the aorta. (c) Dynamic obstruction may occur in ventricular fibrillation or with an ineffective left ventricular beat (Fig. 3C). When the patient is returned to his own circulation, the right ventricle initially may develop a more effective beat than that of the left ventricle. High pressures measured in the left atrium indicate that this may occur after elective potassium arrest.

4. *Overfilling of the pulmonary vascular bed by a combination of the above factors.*

We have analyzed our experiences with more than 140 patients who underwent open-heart operation, and we shall discuss the technical problems that have led to the development of pulmonary complications.

A

Fig. 1. (A) Forward overfilling by increased blood volume of the patient occurs during partial bypass. Increased blood volume in the right atrium is transmitted to the lungs.

Case Reports

Case 1. A six-year-old boy underwent open-heart operation for correction of a large interatrial septal defect. When the heart-lung machine was started and before the venae cavae were tied off, a technical error was made. Although it was promptly corrected, blood was pumped into the venae cavae, distending the right heart and entering the pulmonary arteries. This must have led to rupture of the capillary system in the lungs, since within minutes bloody fluid was recovered from the tracheal tube.

During the subsequent time that the child was maintained on the heart-lung machine, the lungs seemed to recover, and no more blood came from the trachea. However, the damage was done; roentgenograms made shortly after the operation showed many focal densities in both lungs (Fig. 4). The acute changes were consistent with diffuse intrapulmonary hemorrhage and associated edema. A roentgenogram made that evening showed progressively severe changes, and on one made the next day the lungs appeared solidly opaque. The child died in anoxia despite administration of progressively stronger mixtures of oxygen via the positive-pressure (Bennett) respirator.

At necropsy the lungs grossly resembled hepatic tissue, being firm and engorged with blood. A minimum of air-containing tissue was left. Microscopic findings were unusual.

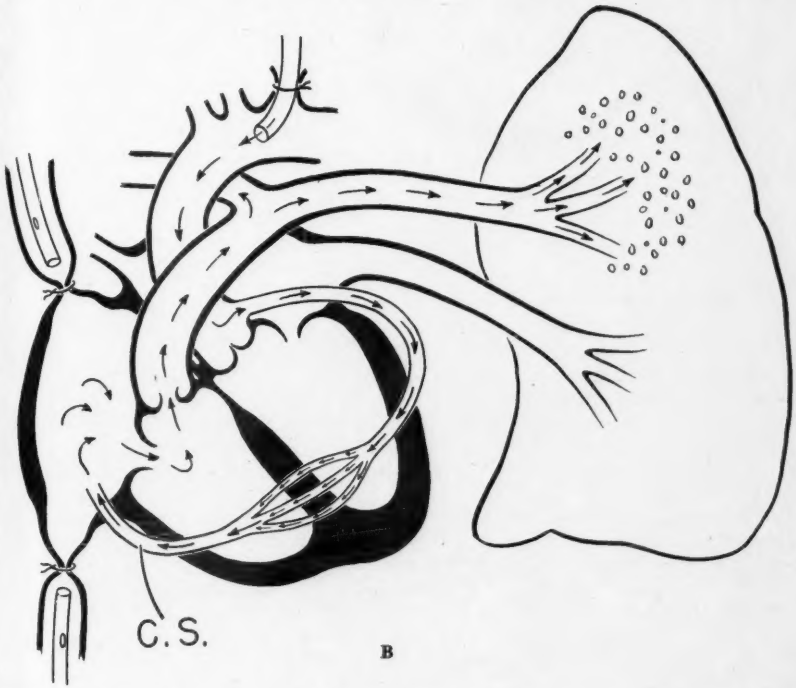
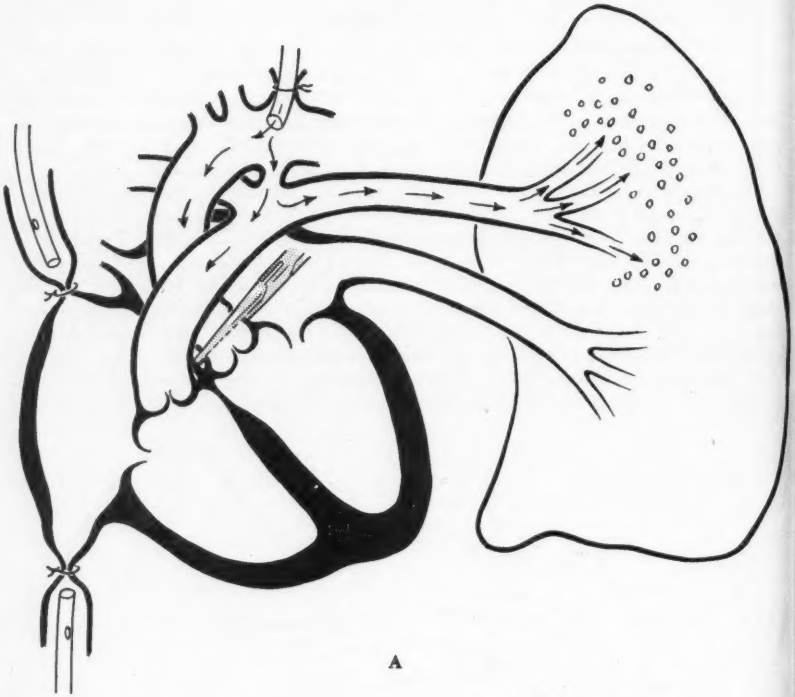


Fig. 1. (**B**) Forward overfilling occurs during total bypass (the venae cavae are tied off). Blood coming from the coronary sinus fills the right atrium, right ventricle, pulmonary artery, and pulmonary vessels.



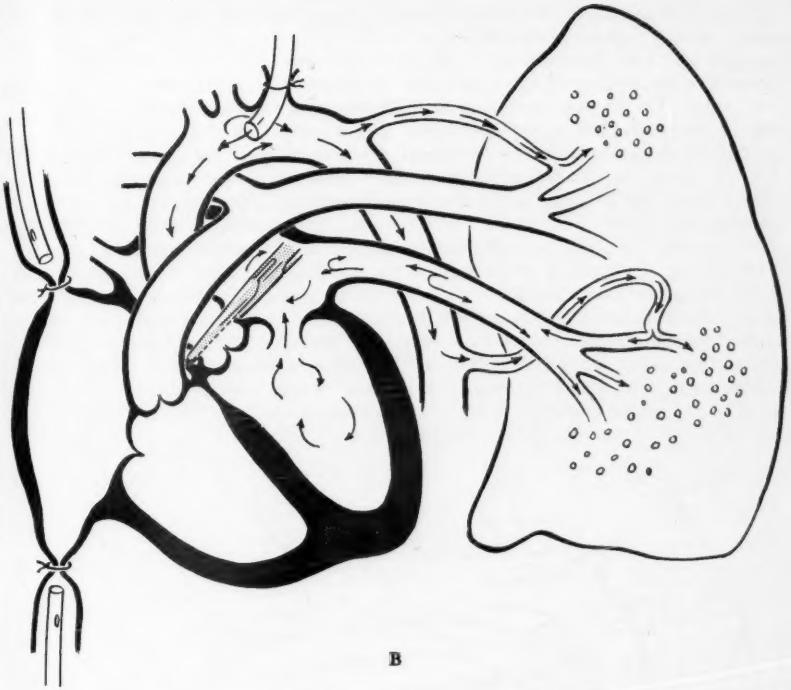
A

Fig. 2. (**A**) Filling of the pulmonary vascular bed occurs through the patent ductus.

In some areas the alveoli were filled with blood; in others there was a mixture of blood, fibrin, and granular coagulin. Elsewhere there were large masses of fibrin in the alveoli. Most striking, however, were large areas where the fibrin coated the alveolar membrane as in hyaline membrane disease of the newborn (Fig. 5). This reminded us of the tragically correct remark made by the child shortly before he died: "I can breathe, but I cannot get the oxygen out."

For this case there exists no doubt concerning the pathogenesis of the changes. They are due to forward overfilling of the pulmonary vascular bed. The progress of the changes could be followed both roentgenographically and clinically. The temporary improvement of the pulmonary changes during the time that the patient was maintained on the heart-lung machine should be kept in mind, and may become of practical importance when heart-lung machines are able to sustain a human being for several days without inflicting damage to the clotting mechanism or to other functions.

Case 2. A 12-year-old boy, who weighed 45 kg., underwent open-cardiotomy with potassium citrate arrest for repair of anomalous drainage of the right pulmonary veins and an interatrial septal defect. Pulmonary arterial pressure was 42/10 mm. of Hg. It was found that the veins of the right upper and middle lobes drained into the right



B

Fig. 2. (B) Filling of the pulmonary vascular bed occurs through the collateral blood vessels.

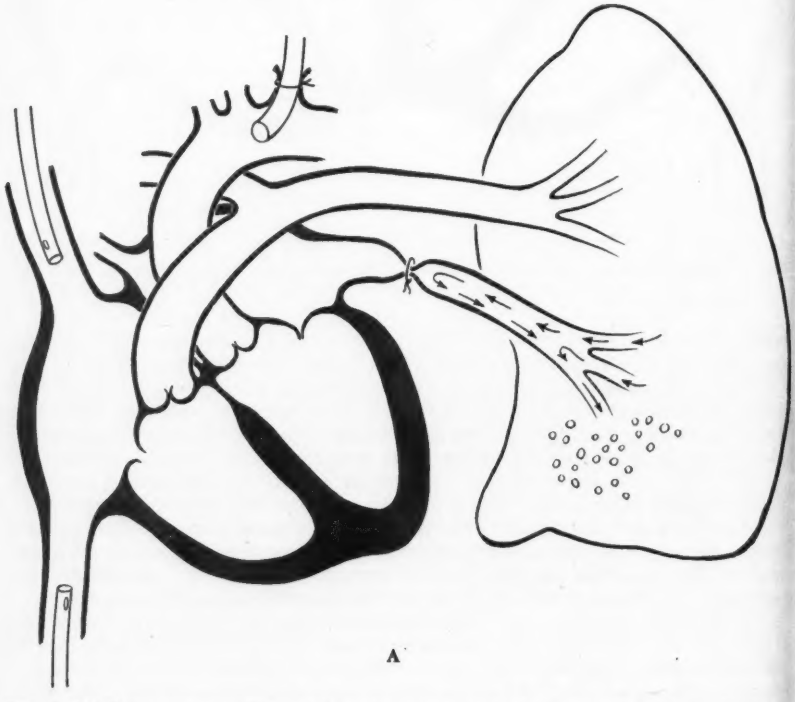
atrium. In order to make them drain into the left atrium, the defect was closed, shifting the atrial wall to the right of the veins.

During the bypass the child was overtransfused with 600 ml. of blood which later was removed. Nevertheless, it could be seen that all of the pulmonary veins were distended and the pressure in the left atrium was palpably high. After the run, the venous pressure was 18 mm. of saline solution, and the mean arterial pressure was low, varying from 40 to 70 mm. of Hg. The postoperative roentgenogram demonstrated massive opacification in the right upper and middle pulmonary lobes and lesser similar changes in the left lung field, probably the result of extravasation of blood (Fig. 6). That evening, fearing thrombosis or mechanical obstruction of the venous drainage, the upper and middle lobes were surgically removed. No mechanical obstruction to the pulmonary veins could be demonstrated. The child died in spite of the pulmonary resection.

At necropsy the same type of engorgement was present in all remaining lung tissue. The microscopic changes of a hemorrhagic pulmonary edema were present in the excised right upper lobe. There was no recognizable fibrin, but a granular coagulum was in the alveoli. Sections of the left lower lobe showed essentially the same changes. The myocardium, while grossly normal, microscopically showed multiple areas of fresh focal necrosis.

It is possible that the pulmonary changes began in the lobes in which the venous outflow was transposed because of some impedance of outflow, but the high left atrial pressure must have been due to left ventricular failure. We consider this to have been retrograde overloading of the pulmonary vascular bed by mechanical and dynamic obstruction. The etiopathogenesis of the myocardial necrosis, undoubtedly the cause of the left ventricular failure, we were unable to determine.

Case 3. A 53-year-old man underwent open cardiotomy for correction of aortic stenosis. While the circulation was maintained with a heart-lung machine, the aorta was clamped and the heart was arrested with potassium citrate for 16 minutes. After correction of the stenosis, a certain degree of aortic insufficiency remained. After the clamp on the aorta was released, blood coming from the heart-lung machine flowed back into the left ventricle, which soon became hard and distended. Ventricular fibrillation occurred and lasted 35 minutes. We assume that in this fibrillating heart the pressure in the left ventricle was further transmitted to the left atrium and, since there was no vent in the left atrium to release it, pressure was built up in the pulmonary veins. The anesthetist noted that bloody fluid came from the endotracheal tube. Many electric shocks were administered before a sinus rhythm became established.



A

Fig. 3. (A) Retrograde overfilling of the pulmonary vascular bed occurs through mechanical obstruction of a pulmonary vein.

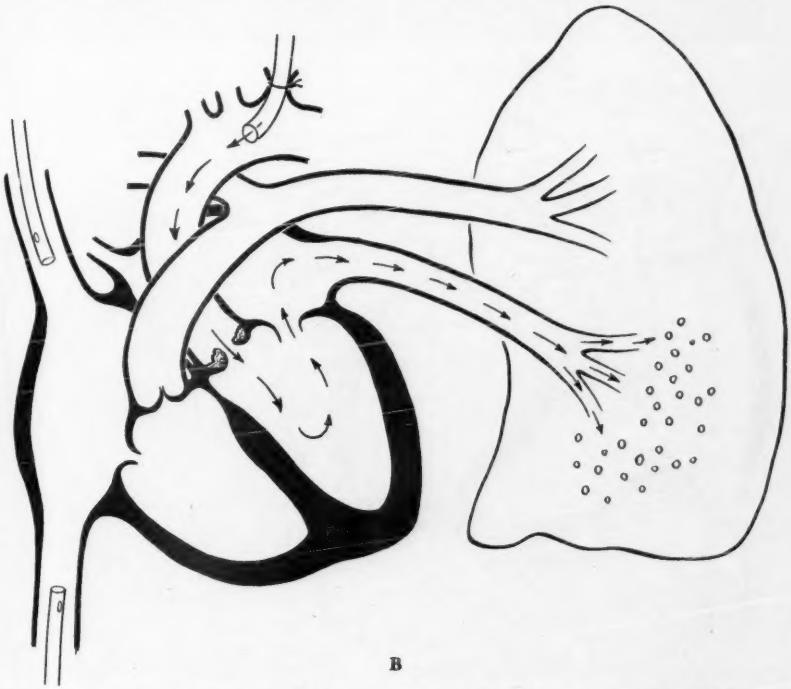
The postoperative chest roentgenogram demonstrated widely distributed areas of increased density bilaterally (Fig. 7). A roentgenogram made several hours later demonstrated progression of the areas of density. In view of the fact that these changes were noted a few hours after the operation, the areas of density probably represented pulmonary hemorrhage as well as pulmonary edema.

This, then, is an example of mechanical (aortic insufficiency) and dynamic (ventricular fibrillation) obstruction. It could have been counteracted if a large drainage tube had been inserted into the left atrium to relieve the pressure.

Case 4. A 9-year-old girl had an interventricular septal defect, severe kyphoscoliosis and mild pulmonary hypertension (47 mm. of Hg). Multiple small hemorrhages in the lungs were observed when the chest was opened. They were considered an indication of a "brittleness" of pulmonary vessels.

After surgical closure of the defect during potassium citrate arrest, the patient had a period of ventricular tachycardia resulting in ineffective circulation that required continued use of the heart-lung machine. An electric shock restored a normal sinus rhythm. In retrospect it seems that backing up of blood in the left side of the heart occurred during the period of arrhythmia which lasted 16 minutes.

Postoperative chest roentgenograms demonstrated an area of moderately increased density involving at least one third of the right lung, the appearance of which is con-

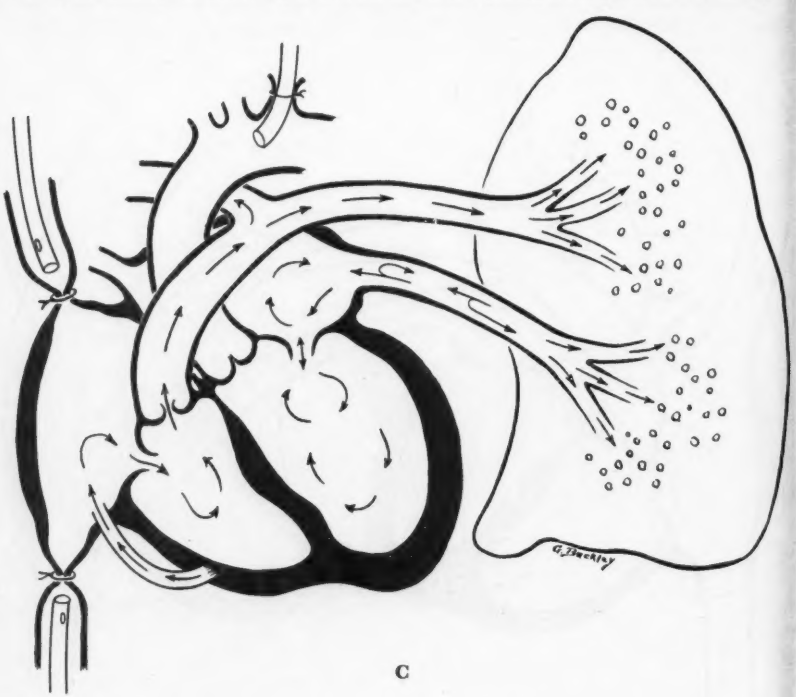


B

Fig. 3. (**B**) Retrograde overfilling of the pulmonary vascular bed occurs because blood from the heart-lung machine flows through incompetent aortic and mitral valves into the pulmonary veins.

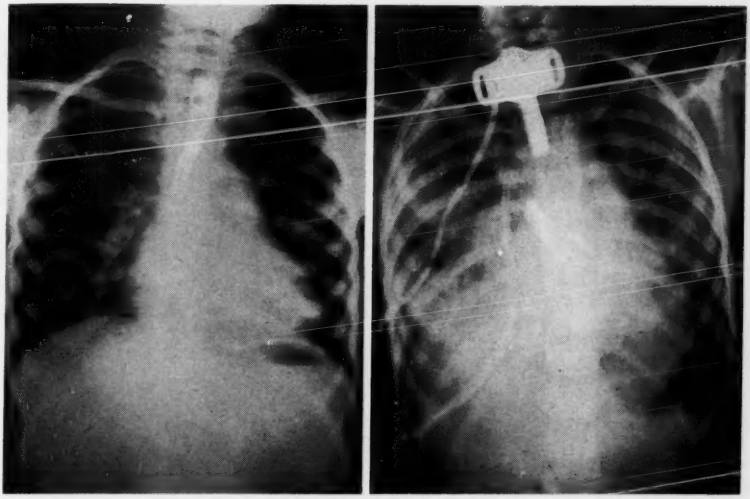
sistent with intrapulmonary hemorrhage (Fig. 8A, B). A roentgenogram four days later showed progression of these changes, which then involved both lungs (Fig. 8C). After a temporary improvement her clinical condition deteriorated. It became increasingly difficult to elevate the blood pH. She became completely dependent on the positive-pressure respirator (Bennett), and died in uremia. The lungs at necropsy were intensely congested. There were focal intraalveolar hemorrhages, and some granular coagula but no fibrin deposits in the alveoli.

Case 5. A 34-year-old man had an interatrial septal defect and high pulmonary artery pressure, 102/46 mm. of Hg. Cyanosis was not present. Pulmonary arteriolosclerosis was proved by lung biopsy. The interatrial septal defect was closed through the opened right atrium. There was no evidence of overloading of the circulation shortly before, during, or after treatment with the heart-lung machine. The duration of cardiac arrest was 13 minutes, and the heart rate restored itself within one minute after release of the aortic clamp. Some air emerged from the puncture hole in the pulmonary artery, after its pressure had been measured, indicating that more may have been present. As there was no catheter in the left atrium, the possibility exists that backing up of blood took place during the recovery phase of cardiac arrest, perhaps enough to initiate changes



C

Fig. 3. (C) Retrograde overfilling of the pulmonary vascular bed occurs because dynamic obstruction due to ventricular fibrillation or inefficient left ventricular beat causes blood from the coronary circulation or from elsewhere to pool in the left ventricle and finally to back up into the pulmonary veins.



A B

Fig. 4. Case 1. (**A**) Preoperative chest roentgenogram shows clear lung fields. (**B**) Roentgenogram made shortly after the operation shows focal areas of increased density throughout both lungs. These acute changes represent diffuse intrapulmonary hemorrhages and associated edema.

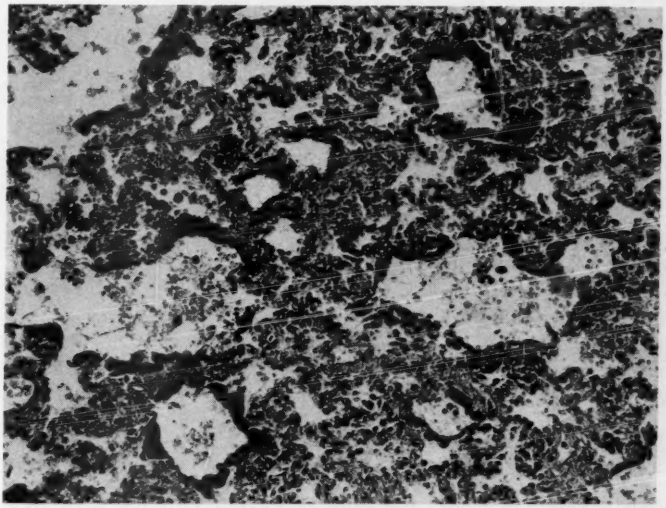
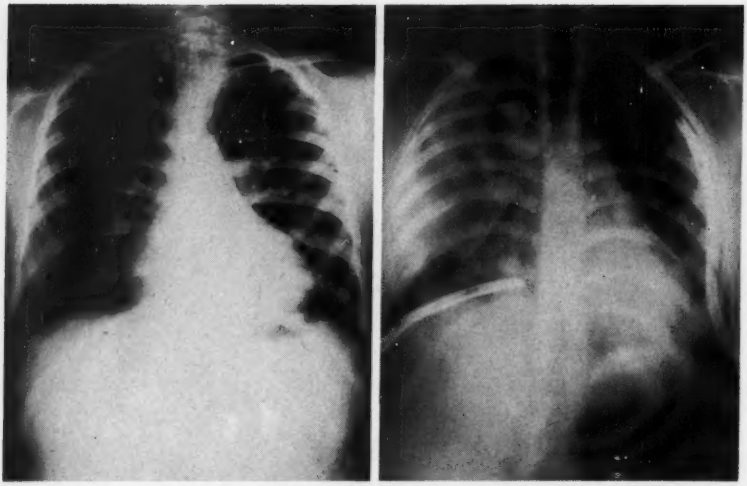
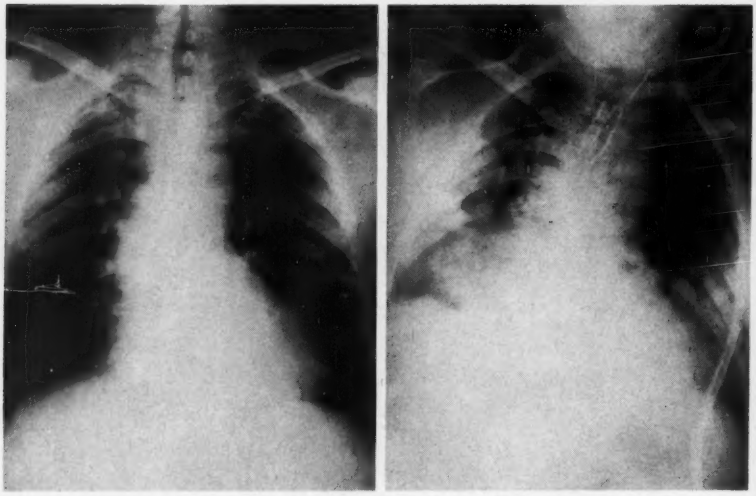


Fig. 5. Case 1. Photomicrograph of lung findings at necropsy: a waxy material, which stains positively with fibrin stains, coats many of the alveolar membranes. Hematoxylin-eosin and methylene blue stain; X 100.



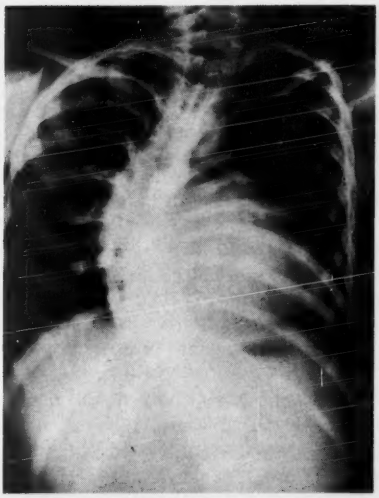
A B

Fig. 6. Case 2. (**A**) Preoperative roentgenogram shows clear lung fields with normal vascular markings. (**B**) Postoperative roentgenogram shows an area of increased density obscuring at least two thirds of the right thorax. Note that lesser changes are also apparent on the left side.

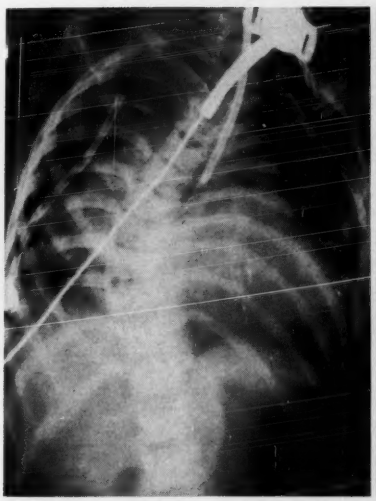


A B

Fig. 7. Case 3. (**A**) Preoperative chest roentgenogram shows cardiac enlargement and clear lung fields. (**B**) Postoperative chest roentgenogram demonstrates areas of increased density bilaterally and widely distributed.



A



B

C

Fig. 8. Case 4 .(A) Preoperative chest roentgenogram demonstrates a marked kyphoscoliosis and probable cardiac enlargement. Lung fields are clear. **(B)** Postoperative chest roentgenogram shows a moderate increase in density involving at least one third of the right lung field, the appearance of which is consistent with intrapulmonary hemorrhage. Two days postoperatively some improvement of the changes in the lower right lung had occurred. **(C)** Progress roentgenogram four days later shows progression of the pathologic changes that now involve both lungs.

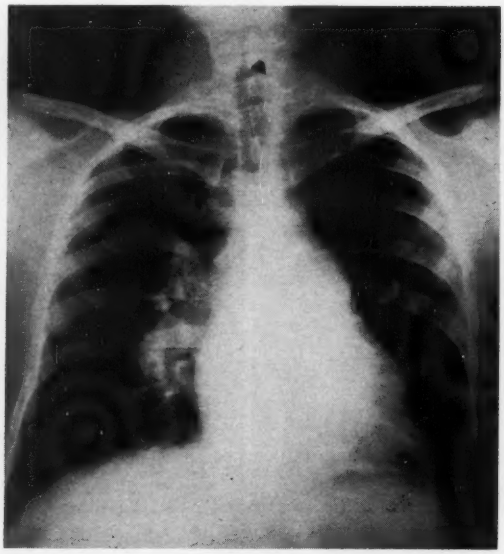
that became more evident the following day (Fig. 9). The immediately postoperative roentgenogram showed no evidence of intrapulmonary hemorrhages, but later, patchy areas of increased density as well as haziness over the left lung were noted. Their development during seven days would tend to indicate extensive edema or inflammatory processes rather than pulmonary hemorrhage. The patient was maintained on a respirator (Bennett) with positive pressure for approximately 14 days, and finally recovered.

This patient was considered a bad operative risk, but was accepted for surgery in view of the poor prognosis without surgical correction. We did not use left atrial decompression at the time. The patient's survival can be attributed to the use of the Bennett respirator.

Avoidance of Pulmonary Complications Due to Overfilling of the Pulmonary Vascular Bed

If the hypothesis is accepted that temporary overloading of the pulmonary circulation can initiate capillary damage in the lungs and a sequence of serious events, every attempt should be made to avoid this overloading, however short the duration.

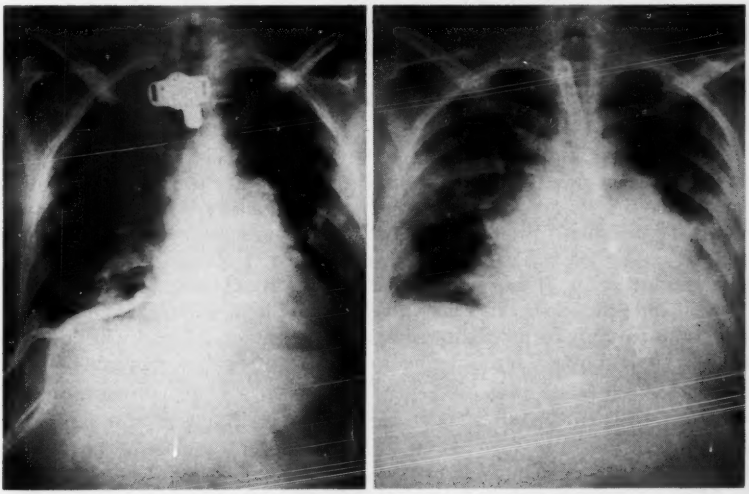
1. *Forward overfilling of the pulmonary vascular bed.* (a) Overfilling by volume changes during partial bypass can be avoided: (1) Rigid maintenance of a



A

Fig. 9. Case 5. (A) A preoperative roentgenogram demonstrates a moderately enlarged heart with prominent pulmonary artery segment and prominent right hilar mass that is considered to be due principally to dilated pulmonary vessels. The periphery of both lung fields as well as the bases are relatively clear.

constant volume of the heart-lung machine will permit increase of the patient's blood volume only by intentional transfusion. The Gibbon type of oxygenator[17,18] and the Clark and Gollan[19] oxygenator have an electronically controlled constant volume. Our own disposable membrane oxygenator[2] has an accurate volume control although it is visually maintained. Mr. Frederick Olmsted has provided our Kay and Cross oxygenator with an automatic volume control. A disadvantage of a rigidly controlled volume of the machine is that blood loss anywhere, unless replaced, will be reflected in decreased output of the artificial-heart pump and, if severe, in reduced circulation, shock, and anoxic changes on the electroencephalogram. We shall accept these disadvantages when overfilling of the vascular bed of the lungs can be avoided with certainty. (2) Prevention of "suck in" is desirable. In some machines, temporary difficulty with venous outflow can lead to negative pressures that suck the walls of the venae cavae into the openings of the venous cannulae, blocking them and leading to volumetric changes. This can be avoided by the use of a venous reservoir in which a slight (4 mm. of Hg) negative pressure is automatically maintained,[17,18] or by the use of an open venous reservoir that can be moved up and down so that the degree of suction can be regulated by the height of the



B C

Fig. 9. Case 5. (B) An immediately postoperative roentgenogram shows no apparent change in the cardiac size or silhouette. Increased markings at the right base are partially due to incomplete inspiration and probably are associated with areas of segmental atelectasis. The left lung though not sharply defined is considered clear. **(C)** A roentgenogram seven days later shows a marked increase in the over-all size of the heart. Patchy areas of increased density and haziness over the chest laterally on the left side are noted. It is apparent that these pulmonary changes have progressed. Their delayed development tends to indicate extensive edema or inflammatory processes rather than pulmonary hemorrhage. Increase in cardiac size suggests probable right heart failure.

siphon.[13] We prefer the latter device. (3) Monitoring of central venous pressure. This is an important safeguard. A rising venous pressure suggests blood-pooling in the caval system. As previously stated, however, during total bypass and when the right heart is open, the lungs are protected against forward overfilling even if the venous pressure is elevated.

(b) Accumulation of coronary sinus blood can occur only when the right side of the heart is closed. Releasing of the caval occlusion may or may not suffice for draining the sinus blood out toward the venous cannula of the heart-lung machine; a cannula in the right atrium itself may be necessary, according to animal experiments conducted by Dr. T. A. Akutsu in our laboratory.

2. *Filling of the pulmonary vascular bed through collateral vessels.* An open ductus must be closed before starting, or at the onset of, extracorporeal circulation. Increased bronchial circulation may lead to a large influx of blood into the lungs. We no longer believe that maintenance of free reflux through the pulmonary valve into the open right ventricle provides adequate decompression of the pulmonary circulation; we currently prefer to have a cannula in the left atrium to drain off the excess blood.

3. *Retrograde overfilling*, whether mechanical (obstruction) or dynamic (fibrillation or insufficient left ventricular contraction). A large cannula in the left atrium can prevent retrograde overfilling except that which is due to obstruction of a pulmonary vein (Fig. 10). This cannula is easily inserted from the right side immediately behind the junction of the right atrium and posterior atrial septum.

A blood-filled U tube connected to the cannula indicates the pressure in the left atrium. When there is obstruction, the pressure in the left atrium in a few seconds may rise to 50 cm. or higher on the manometer. Under such circumstances the cannula is promptly vented to the venous reservoir which is under the level of the heart. A constant flow of bright-red blood will be observed if there is obstruction. *Warning:* Negative pressure should not be applied to the cannula while the left heart is open to the atmosphere, even if it is only via an open foramen ovale to the right atrium, because residual blood will be sucked out and replaced by air, resulting in air embolism when the heart beats.

Discussion

As already mentioned, the problems of acidosis and overoxygenation have been recognized. Pulmonary complications in a given case may result from any combination of errors relative to acidosis, excessive oxygenation, and overfilling of the left heart. Although we do not have experimental evidence to support this concept, it is possible that the metabolic changes associated with excessive oxygenation may promote pulmonary vascular fragility and, in turn, make the lungs susceptible to damage from relatively mild overfilling of the vascular bed.

There seem to be cases where each of the above-listed factors played a role in the development of pulmonary lesions.

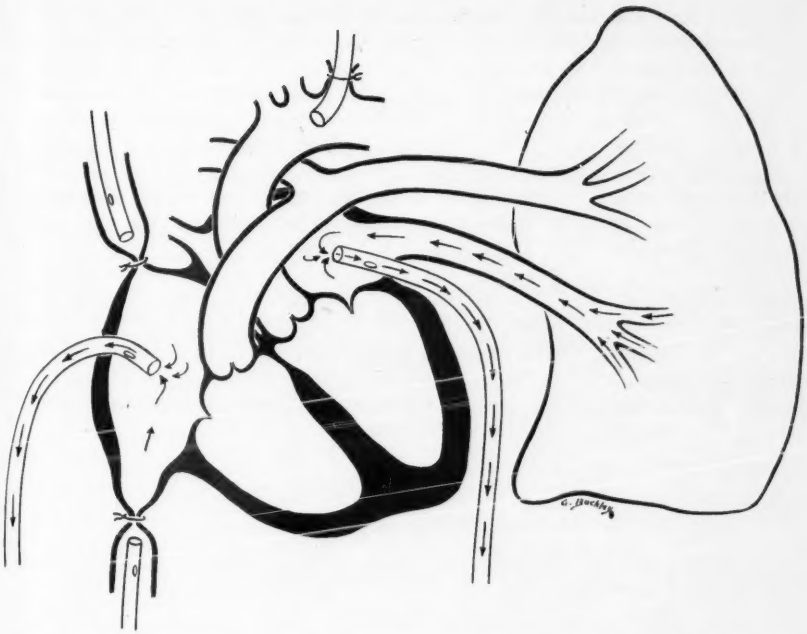


Fig. 10. Safeguard against overfilling of the pulmonary vascular bed: a cannula is in the left atrium. Another cannula in the right atrium may be indicated when the right heart is not opened and the cannulae in the venae cavae do not provide sufficient decompression of the right atrium. This latter cannula has not been used clinically. *Warning:* suction on either cannula when the heart is open must be avoided as it may introduce air into the heart cavities.

Overfilling of the pulmonary vascular bed during operations using extracorporeal circulation is most likely to occur when heart chambers are not open. It can be avoided by placing an adequate drainage tube in the left atrium. After discontinuing the extracorporeal circulation, this same tube should be used to measure the pressure in the left atrium, in order to facilitate recognition of left ventricular failure. Elevated left atrial pressure may indicate that the left ventricle is not ready yet to take over the burden of the circulation.

Summary and Conclusion

The thesis is developed that temporary overloading of the pulmonary circulation with blood is the most important single factor in the initiation of capillary damage that marks the beginning of severe pulmonary complications after open-heart operations.

Pathogenic factors in pulmonary complications are: Pre-existing pulmonary vascular disease; oxygen intoxication of the alveolar and capillary cells from undiluted oxygen administered by the anesthetist when there is no blood going through the bypassed lungs; exsiccation of the lungs as a result of their being continuously ventilated during this period. Small children are more susceptible to having pulmonary complications. Use of too much fluid predisposes to pulmonary edema. Air embolism forming slush in the pulmonary capillary bed will increase the resistance in certain areas in the lungs, but the authors believe that temporary overloading of the pulmonary circulation with blood is the most important factor.

Schema of overloading of the pulmonary circulation:

1. By forward overfilling
   (a) During partial bypass if a sudden increase in the patient's blood volume occurs
   (b) During total bypass by accumulation of extravagant coronary sinus blood in the right side of the heart
2. Through collateral vessels
   (a) Patent ductus
   (b) Increased bronchial circulation
3. By retrograde overfilling
   (a) By mechanical factors
      (1) Pulmonary venous obstruction
      (2) Mitral stenosis
      (3) Aortic and mitral regurgitation
   (b) Dynamic obstruction
      (1) Ventricular fibrillation
      (2) Ineffective left ventricular beat

Acknowledgment

We wish to acknowledge the assistance of Dr. Harold F. Knight, Jr., Dr. William V. Martinez, Dr. Durval F. de Castro, Mr. Janis Eglajs, and Miss Rose Litturi.

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ELECTRONIC CARDIAC PACEMAKER AFTER OPEN-HEART OPERATIONS

Report of a Case of Tetralogy of Fallot with Atrioventricular Block That Reverted to Sinus Rhythm

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SINCE the advent of open-heart operations, surgical damage to the conduction system during operation has become prevalent. Complete atrioventricular (AV) block cannot always be avoided and has been a factor contributing to mortality, either immediately after the operation or later. Now, complete AV block has become reversible by means of cardiac pacemakers. A cardiac pacemaker provides a rhythmic electric stimulus to the ventricles to increase the ventricular rate. If the stimulus is adequate, the ventricles accept the rhythm imposed by the pacemaker, provided that it is faster than the intrinsic ventricular rhythm. Experimentally, in a dog with a sinus rhythm of 85 beats per minute, a heart rate of 90 can be imposed by the pacemaker, but not a rate lower than 85 (Fig. 1). In a dog with heart block and a ventricular rate of 40, any rate in excess of 40 can be imposed.

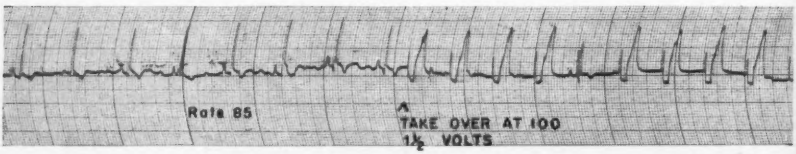

Fig. 1. Electrocardiogram of a dog in which were implanted myocardial electrodes. A normal ventricular rate of 85 was supplanted by an imposed pacemaker rate of 100.

Zoll[1] has designed a pacemaker for use with external electrodes. He advocates this mainly for treatment of diseases such as heart block with Stokes-Adams syndrome. Burchell[2] uses a pacemaker with external electrodes to maintain the ventricular rate in patients who have AV block after open-heart operations.

Allen and Lillehei[3] use a pacemaker that is connected to one electrode on the myocardium and to one under the skin. They have lost only one patient from AV block, of 40 consecutive patients who underwent open-heart operations. That patient, a child, died after he himself tore out the myocardial electrode. Allen and Lillehei[3] have noted that in most cases of surgical AV block the heart regains a normal sinus rhythm if the patient is maintained for a few days at an

This work was supported by a grant to Doctor Kolff from the Cleveland Area Heart Society.

adequate ventricular rate by the pacemaker. Even if the sinus rhythm cannot be restored and the ventricular rate is to remain permanently slow, the heart has adequate time to adjust to the new slow rate.

One elaborate pacemaker[4,5] amplifies the sinus (P) waves with transistors and a hearing-aid battery; the artificial impulse is applied directly to the ventricles.

An increase in ventricular rate, notwithstanding heart block, can be obtained in some patients by administration of chronotropic drugs, such as, isopropylarterenol hydrochloride. Some patients, however, are quite refractory to the drug, or become so, and an adequate cardiac output can be attained only by electric stimulation.

To undertake open-heart operations without a pacemaker at hand no longer seems justifiable. We use the pacemaker described below, when AV block is recognized during the operation.

Description of Electronic Pacemaker

The internal electrodes are made of 26-gauge stainless-steel stranded wires 15/1,000 inch in diameter coated with Teflon* except for the tips. When in use, the electrodes are sutured against the ventricular myocardium in two places. This has the advantages that low current and voltage can be used and that even if one electrode does slip out, it can be placed on some other part of the body and the other electrode still can drive the heart.

The circuit of the pacemaker is designed to meet three requirements (Fig. 2). The terminals to be used on the patient are carefully isolated by an output transformer for the possibility of line-voltage connection. The output impedance is low, matching that of the myocardium, in order to avoid distortion of the wave contour in the myocardium and to insure that the stimulus voltage is that indicated by the control setting. The shape of the stimulus wave is a round-topped spike of less than a millisecond in duration and is rectified so that it is completely monophasic.

A conventional regulated power supply is led to a multivibrator; its frequency (stimulus rate) is controlled by a variable grid bias. The multivibrator activates a neon indicator lamp, the signal is then rectified and is applied to a power tube. The output from this tube is connected by an isolation transformer through another rectifier to the patient.

Case Report

The patient was a 5½-year-old girl who had tetralogy of Fallot. When she was one and one-half years old, she underwent operation for relief of severe anoxic episodes,

Manufactured by Falls Hollow Staybolt Company, Cuyahoga Falls, Ohio.

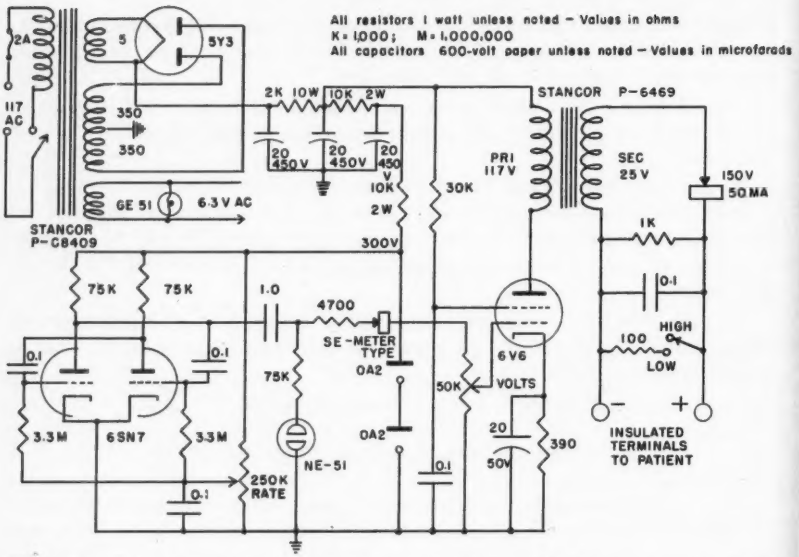

Fig. 2. Schematic diagram of an electronic pacemaker designed for direct connection to the ventricular wall.

comprising a Potts anastomosis* between the pulmonary artery and the aorta. Postoperatively, however, there were some cyanosis, and clubbing of the fingers. At the time of examination at the Cleveland Clinic, cardiac catheterization studies were instituted and pressures in the right ventricle were found to equal those in the left. Movie films made with the Philips image amplifier disclosed a high interventricular septal defect, severe infundibular stenosis, valvular pulmonic stenosis, and 60 per cent dextroposition of the aorta. It was decided to close off the Potts anastomosis and to attempt intracardiac repair using the open-heart approach.

During the operation the patient was maintained with extracorporeal circulation by means of a 13-inch Kay and Cross oxygenator** and a nonocclusive roller-type plastic tube pump at a flow rate of 90 ml. per kilogram of body weight per minute. The total duration of the run was 48 minutes; the duration of total bypass was 32 minutes; the heart was arrested for 24 minutes. Since it was not possible to estimate the time required to close the Potts anastomosis, two arterial cannulae were used, one in the subclavian artery and one in the left common femoral artery, so that even if the aorta had to be clamped on both sides of the anastomosis, both upper and lower parts of the body still would be able to receive blood. In addition to the usual cannulae placed in the venae cavae, another cannula was placed in the left atrium to control any possible build-up of back pressure in the pulmonary veins.

After the artificial heart-lung had been started, the Potts anastomosis was carefully isolated and closed with a double silk ligature. Then the heart was electively arrested with potassium citrate solution. The right ventricle was opened from its midpoint to the

Performed by Dr. Willis Potts, Children's Memorial Hospital, Chicago, Illinois.

**Manufactured by Pemco, Inc., 5663 Brecksville Road, Cleveland 31, Ohio.*

annulus of the pulmonary valve, which was incised to relieve the valvular stenosis. A large mass of abnormal muscular tissue was sharply dissected from the ventricular septum and the anterior wall of the ventricle. The interventricular septal defect, about ⅞ inch in diameter, was closed by an oval patch of Ivalon sponge carefully attached with 12 interrupted sutures. After closure of the ventricular incision, the clamp was removed from the aorta, and the heartbeat started within one minute; however, total AV block was present. The ventricular rate was adequate, but, since we knew from previous experience that it might decrease later, the stainless-steel ends of the two fine electrodes were sutured to the ventricular wall on both sides of the heart and were brought out through stab wounds for connection to the pacemaker. A short trial proved that the pacemaker was able to supplant the ventricular rhythm. The postoperative course was uneventful except for the symptoms of heart block which are described below.

At 12:00 noon, immediately after operation, the patient's heart rate was first maintained with the pacemaker at a rate of about 80. A postoperative chest roentgenogram showed the two electrodes to be in position on both sides of the heart (Fig. 3). At 5:20 p.m.

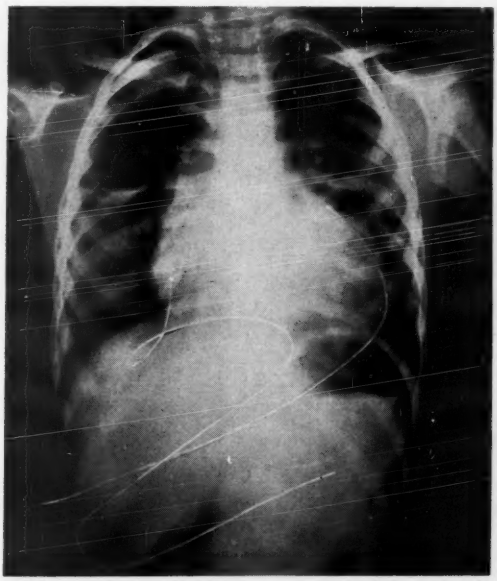

Fig. 3. Postoperative chest roentgenogram that shows the thin stainless-steel (Teflon-coated) wires on either side of the heart, where they are sutured against the myocardium.

that day the pacemaker was disconnected because the patient was able to maintain a heart rate between 70 and 80, although there still was a total block. During the night, however, the pulse rate gradually decreased to 60; the following morning, when it had decreased to 54, she was returned to pacemaker stimulation. The rate was set for between 80 and 90 beats per minute.

The preoperative electrocardiogram is shown in (Figure 4, *1*). That taken while the pacemaker was functioning showed that the ventricular rate of about 85 usually followed

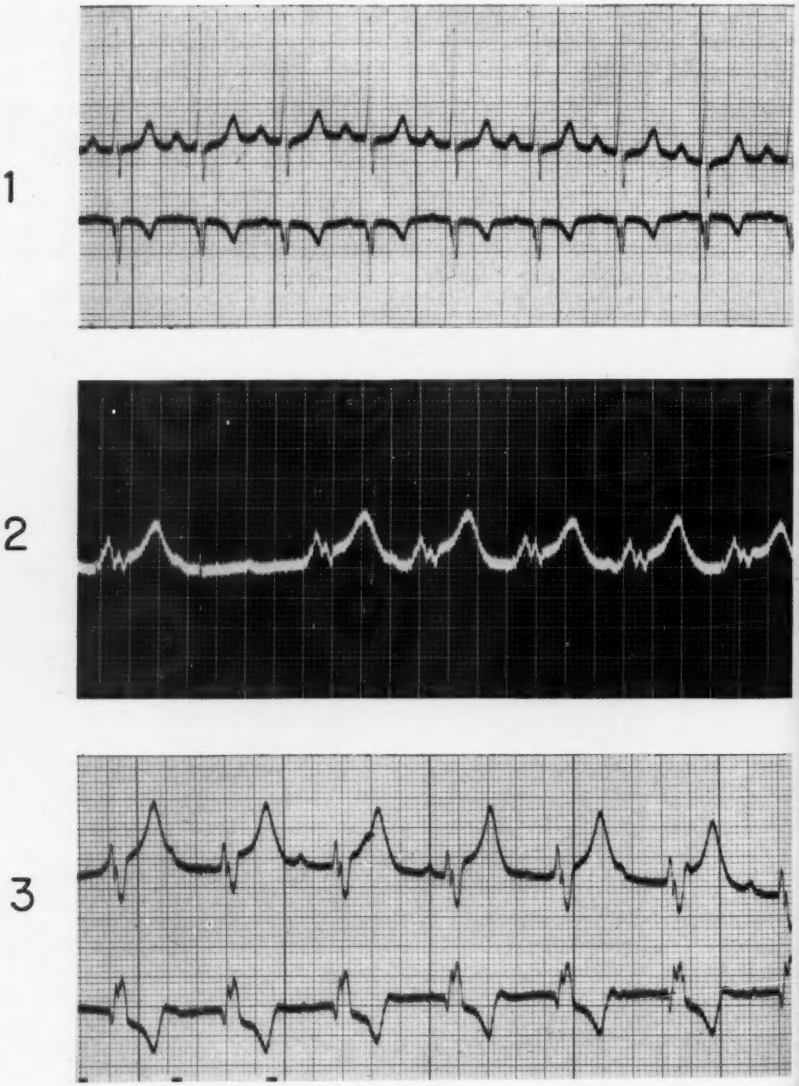

Fig. 4. Electrocardiograms: (1) immediately preoperative—sinus rhythm rate was 100; (2) first postoperative day—ventricles follow pacemaker at a rate of 83 except for one missed beat; (3) fourth postoperative day—AV block; ventricular rate was 80.

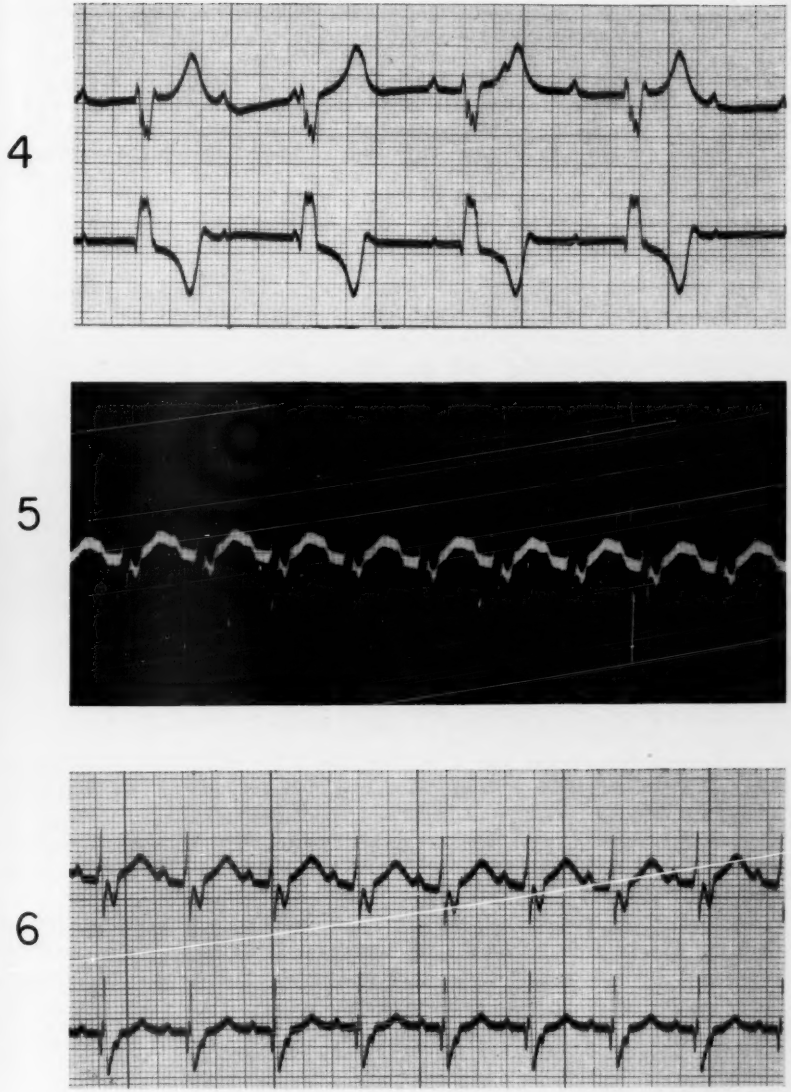

Fig. 5. Postoperative electrocardiograms: (4) seventh day—AV block; ventricular rate decreased to 55; (5) twelfth day—a high ventricular rate of 115 was outrunning the pacemaker that had been set at about 80; it proved to be the sinus rhythm; (6) thirteenth day—heart rate had decreased to 100 beats per minute.

with but an occasional missed beat (Fig. 4, *2*.). On the second day after operation the patient became restless if the pulse did not follow the pacemaker, or when the pulse fell to between 48 and 50 while the pacemaker was off. The voltage of the pacemaker had to be increased to 7 volts (from 5 volts) to obtain a pulse rate of 80 in response to an electric pulse rate of 88. On the third day after the operation the pacemaker was removed because with or without it an idioventricular rate of 80 was maintained. The electrocardiogram made on the fourth postoperative day revealed a total AV block with a ventricular rate of about 80 (Fig. 4, *3*). For the next few days the patient's clinical condition was satisfactory, although the electrocardiograms consistently showed a complete AV block with a ventricular rate of about 80. However, on the eighth postoperative day the ventricular rate decreased to 64. An electrocardiogram made on the eleventh postoperative day still showed complete AV block with a ventricular rate of about 55 (Fig. 5, *4*); at 2:30 p.m. the pacemaker was reconnected to obtain a ventricular rate of about 80. Cessation of the pacemaker caused return to complete AV block with a heart rate of about 54. At 11:00 a.m. on the twelfth postoperative day the patient suddenly had a pulse rate of 100 while the pacemaker was set to maintain a ventricular rate of 80. An electrocardiogram revealed a sinus rhythm with a ventricular rate of 115, which made the pacemaker superfluous (Fig. 5, *5*). The heart rate slowed down during the following days, as shown on an electrocardiogram made on the thirteenth day (Fig. 5, *6*).

By this time the patient's general condition was excellent. She was extremely gay and happy, and moved freely about in the bed with the wires trailing behind her. There was no evidence of myocardial insufficiency. The electrodes were withdrawn from the heart simply by removing the surgical tapes that held them to the chest and then pulling them out. The patient was discharged on the eighteenth postoperative day.

During the twelve days in which the pacemaker was intermittently used, it became necessary gradually to increase the impulse from 5 to 16 volts. The patient seemed to be unaware of the electric impulse at all times.

Summary

Experience with the course of open-cardiotomy patients with heart block leads us to recommend that electrodes be placed on the heart of any patient in whom atrioventricular block occurs during operation, even though the ventricular rate appears to be satisfactory at the time. The cardiac pacemaker should be used in children whose ventricular rates fall below 90, and in adults whose rates drop below 80.

A cardiac pacemaker with internal electrodes was used successfully on a postcardiotomy patient whose 12-day, complete heart block was carried to recovery. It is recommended that a cardiac pacemaker be available at the time that all intracardiac operations are performed.

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THE EFFECT OF IPRONIAZID OINTMENT ON TROPHIC ULCERS ASSOCIATED WITH RAYNAUD'S PHENOMENON

A Clinical Note

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TROPHIC ulcers of the finger tips may occur as a complication of Raynaud's phenomenon. Usually they are painful and cause considerable discomfort. In general, therapy is unsatisfactory. Although sympathectomy often results in healing of the ulcers, they are likely to recur. Medical treatment with vasodilators and blocking agents are of questionable value.[1] The local application of glyceryl trinitrate has been reported[2] to be effective in the relief of Raynaud's phenomenon, though an annoying headache may occur as a side effect of treatment.[3] In our experience this treatment has had little influence on gangrenous ulcers.

During the past five years we have used iproniazid* ointment, from 2 to 5 per cent in a water-soluble base, in the treatment of 23 patients. This group consisted of 14 patients with progressive systemic sclerosis and five patients with acrosclerosis complicated by ulceration of the finger tips, two patients with systemic lupus erythematosus in whom painful ulcerations appeared over interphalangeal joints, and two patients with advanced Raynaud's disease in whom painful ulcerations of the finger tips developed within six months and one year, respectively, after sympathectomy.

The ointment was applied twice daily to the ulcers, and the fingers were wrapped lightly with gauze. Within from 24 to 72 hours pain disappeared, and after a few weeks the ulcers usually healed (Fig. 1). Of the group of 23 patients, 19 had complete relief of pain, and 18 had complete healing of the ulcers. However, eight patients had recurrence of pain and ulcers within from three weeks to six months after temporary discontinuation of the treatment.

Intolerance to local applications of the ointment has not developed, and no complications from this medication have been observed. The mechanism responsible for the relief of pain as well as for the stimulation of healing of the ulcers has not been determined.

**Marsalid phosphate, Hoffmann-LaRoche, Inc. The material for this study was supplied through the courtesy of Hoffmann-LaRoche, Inc., Nutley, New Jersey.*

A

B

Fig. 1. (**A**) Painful trophic ulcerations over the proximal interphalangeal joints of a 24-year-old woman who had severe progressive systemic sclerosis. (**B**) Complete healing of ulcers 19 days after 3 per cent iproniazid ointment was applied twice daily. Pain diminished within 24 hours after the ointment was applied.

Summary

1. Trophic ulcers associated with Raynaud's phenomenon are painful and often difficult to treat.

2. In a series of 23 patients who had trophic ulcers occurring as a complication of Raynaud's disease or secondary Raynaud's phenomenon, the application of iproniazid ointment often resulted in decrease of pain and healing of the ulceration. When treatment was discontinued, pain and ulceration sometimes recurred.

3. The pharmacologic action has not been determined.

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FURTHER OBSERVATIONS ON THE USE OF 4-AMINOQUINOLINE COMPOUNDS IN PATIENTS WITH RHEUMATOID ARTHRITIS OR RELATED DISEASES

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and

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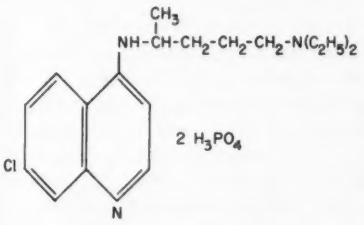
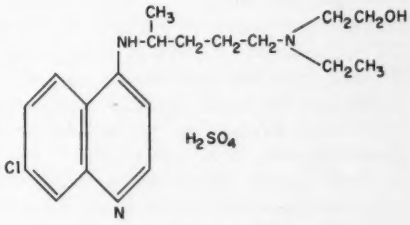
A NUMBER of investigators[1-11] have reported that in patients with rheumatoid arthritis and allied diseases, clinical improvement occurs after administration of the 4-aminoquinoline compounds, chloroquine phosphate and hydroxychloroquine sulfate.** In a previous report[11] the effect of hydroxychloroquine sulfate was compared with that of chloroquine phosphate in patients with rheumatoid arthritis. It was concluded that hydroxychloroquine sulfate in equal dosage caused fewer drug reactions than did chloroquine phosphate; however, in such dosage, hydroxychloroquine sulfate was less effective as an anti-inflammatory agent. The purpose of this report is to describe the results that were observed during the past three years in the administration of these compounds, alone or in combination with other agents, to 805 patients with rheumatoid arthritis or related diseases.

Drugs Used

Chloroquine phosphate is 7-chloro-4 (4-diethylamino-1-methylbutylamino) quinoline diphosphate. Hydroxychloroquine sulfate is 7-chloro-4-[4-(N-ethyl-N-β-hydroxyethylamino)-1-methylbutylamino] quinoline sulfate. The structural formulas are:



Chloroquine phosphate



Hydroxychloroquine sulfate

Special Fellow in the Department of Rheumatic Disease.

***Chloroquine phosphate (Aralen), and hydroxychloroquine sulfate (Plaquenil), used in this study were supplied through the courtesy of Winthrop Laboratories, New York, New York.*

Read at the Ohio regional meeting of The American College of Physicians, Jan. 23, 1958, Cleveland, Ohio.

Hydroxychloroquine sulfate is similar to chloroquine phosphate except that a hydroxyethyl group has been substituted for an ethyl group on the tertiary amino nitrogen. Both drugs are almost completely absorbed from the gastrointestinal tract, although hydroxychloroquine sulfate apparently is absorbed more rapidly than is chloroquine phosphate. Considerable amounts of the drugs are found in the liver, spleen, kidneys, lungs, skin, and leukocytes, while the lowest concentration is in the central nervous system. Approximately 25 per cent of the oral daily dose is excreted in the urine, and after administration has been discontinued, the remainder of the drugs slowly undergoes metabolic degradation.

Selection of Patients

Of 805 patients treated with one of the 4-aminoquinoline compounds, 716 patients had arthritis of the rheumatoid type, of which 627 had typical rheumatoid arthritis, 53 had arthritis of the rheumatoid type with a positive test for lupus erythematosus, 23 had rheumatoid arthritis with psoriasis, and 13 had juvenile rheumatoid arthritis. Eighty-nine patients had other disorders of the connective tissue, including arteritis, dermatomyositis, progressive systemic sclerosis (scleroderma), Reiter's syndrome, and systemic lupus erythematosus.

The results of treatment in these patients will be reported later, but the incidence and the variety of drug reactions that occurred from the use of chloroquine phosphate and hydroxychloroquine sulfate in the total group of 805 patients are included in this report. Of the 716 patients, 487 were treated for periods of from one to three years. Because of the characteristic instability of the course of rheumatoid arthritis, results of treatment include data from only those patients who were treated longer than one year.

Dosages and Administration of Drugs

Chloroquine phosphate is available in tablets of 125 mg. and of 250 mg. Originally an initial dose of 500 mg. daily was administered, which was reduced to 250 mg. as improvement was noted. Gastrointestinal reactions occurred in about 30 per cent of the first patients treated, and it was found that by reducing the initial dose the incidence of gastrointestinal reactions decreased. About 12 per cent of the patients did not tolerate an initial dose of 250 mg. of chloroquine phosphate daily; they were given 125 mg., and after two months an attempt was made to increase this to 250 mg. daily. At the present time we are recommending that the maximum daily dose of chloroquine phosphate be 250 mg. daily.

Hydroxychloroquine sulfate is available in coated tablets of 200 mg. In equal dosages we have found hydroxychloroquine sulfate to be approximately from one half to two thirds as potent as chloroquine phosphate (600 mg. of hydroxychloroquine sulfate is approximately as effective as 250 mg. of chloroquine phosphate), while the incidence of drug reactions is approximately one half that of chloroquine phosphate. Originally we administered up to 1.0 gm. daily in divided doses with or after meals, but the larger doses did not hasten initial improvement.

Although the incidence of drug reactions was less than that occurring from chloroquine phosphate, the reactions still remain a problem. Consequently, the initial dosage of hydroxychloroquine sulfate was reduced to 600 mg. daily, administered in divided doses with or after meals. After major improvement (grade I or grade II response*) had been maintained for at least one year, the dosage of hydroxychloroquine sulfate was reduced to 400 mg. daily in divided doses taken with or after meals.

Sixteen children have been included in this study. For those who weighed approximately 15 kg. the usual daily dose was 125 mg. of chloroquine phosphate, or 200 mg. of hydroxychloroquine sulfate. Two children who weighed 10 kg. and 12 kg., respectively, received 125 mg. of chloroquine phosphate on alternate days. With one exception all of the children have continued to receive maintenance doses of one of the drugs after from one to three years of treatment. One child with active rheumatoid arthritis of one year's duration was given chloroquine phosphate (125 mg. daily) for one year, at which time a remission occurred. Chloroquine phosphate was continued for six more months and then was discontinued. The child's disease has remained in remission for two years since chloroquine phosphate therapy was stopped.

Clinical Response to Therapy

Previously the results of therapy were reported with 4-aminoquinoline compounds in 51 adult patients who were observed for 18 months.[11] Of 26 patients who received hydroxychloroquine sulfate, 23 tolerated the drug and 15 of those obtained major improvement. Of 25 patients who received chloroquine phosphate, 19 tolerated the drug and 12 obtained major improvement. There was no direct correlation between the response to therapy and the stage or the duration of the disease, or the patient's functional capacity.

Since the previous report, an additional 63 patients have been treated with an antimalarial compound as the sole therapeutic agent. Eight patients from our original group have been lost to follow-up study; 60 patients are receiving hydroxychloroquine sulfate and 46 are receiving chloroquine phosphate (Table 1).

Response to therapy in this group resembles that in our original group. Of those patients who received hydroxychloroquine sulfate, 60 per cent had grade I or grade II response; of those who received chloroquine phosphate, 62 per cent had a similar response. Again it was observed that little or no correlation existed between response to therapy and stage of disease, functional capacity of the patient, or duration of the disease. We have found a better correlation between response to therapy and the serum polysaccharide-protein ratio[13] as a measure of disease activity than we have with any other test now available. The majority of patients who obtained major improvement had serum polysaccharide-protein ratios of 2.55 or less. No patient with a serum polysaccharide-protein ratio of 2.80, or greater, obtained major improvement while receiving one of the 4-aminoquinoline compounds as the sole therapeutic agent. Nonarticular features

*A.R.A. classification[12].

of the disease, including weakness, emotional instability, loss in weight, and vasomotor reactions, usually were not severe.

We believe that it is important to emphasize the subtle manner in which clinical improvement often occurred, since it did not become obvious in many patients until they had been treated for one year or longer.

Table 1. — *Results of hydroxychloroquine sulfate and chloroquine phosphate therapy for rheumatoid arthritis in 106 patients*

Drug	Number of patients	Stage* of disease	Class** of functional capacity (Number of patients) I	II	III	IV	Duration of disease at onset of therapy	Grade† of response after from 1 to 3 yrs. of therapy (Number of patients) I	II	III	IV
Hydroxychloroquine sulfate	14 (17-3††)	I	1	3	7	3	3 mos. to 26 mos.	4	7	2	1
	20 (22-2††)	II	0	8	10	2	16 mos. to 4 yrs.	5	5	8	2
	16	III	0	3	8	5	2 yrs. to 12 yrs.	3	6	7	0
	10	IV	0	2	6	2	3 yrs. to 18 yrs.	1	5	3	1
Total	60 (65-5††)		1	16	31	12		13	23	20	4
Chloroquine phosphate	13 (14-1††)	I	0	5	6	2	5 mos. to 3 yrs.	6	7	1	0
	11 (13-2††)	II	0	4	6	1	11 mos. to 8 yrs.	3	4	2	2
	12	III	1	5	5	1	2 yrs. to 16 yrs.	1	4	6	1
	10	IV	0	3	5	2	3 yrs. to 26 yrs.	1	3	4	1
Total	46 (49-3††)		1	17	22	6		11	18	13	4
Total	106		2	33	53	18		24	41	33	8

A.R.A. Classification.[12]

**Stage:* I — *Joint swelling, no joint destruction;* II — *minimal cartilage or bone destruction;* III — *subluxation;* IV — *ankylosis.*

***Class:* I — *asymptomatic, full activity;* II — *minor symptoms, adequate activity;* III — *moderate-to-severe symptoms, limited activity;* IV — *severe symptoms, near or complete incapacitation.*

†*Grade:* I — *complete remission;* II — *major improvement;* III — *minor improvement;* IV — *no improvement, or progression of disease.*

††*Patients lost to follow-up.*

Initial response. The onset of clinical improvement usually was delayed for from six weeks to three months, when it began slowly and progressed irregularly over a period of from six to 12 months. Rarely was maximum improvement delayed beyond 12 months. After the first month of therapy only 22 patients

(21 per cent) of the 106 had attained grade I or grade II response; after three months 50 patients (47 per cent) were similarly improved. After six months, 57 patients (54 per cent), and after one year 65 patients (62 per cent) were asymptomatic. Thirty-three patients (30 per cent of the group) had grade III response to therapy, and eight patients (8 per cent) had grade IV response (Table 1).

Persistence of disease fluctuations. One of the most characteristic features of rheumatoid arthritis is fluctuating disease activity. This feature of the disease persisted and was modified but was not eliminated by the administration of 4-aminoquinoline compounds. Exacerbations became less severe and of shorter duration in those patients who eventually attained major improvement, while periods of relative freedom from most musculoskeletal manifestations increased in duration. Eventually the exacerbations were manifested only by periods of weakness or of exhaustion which lasted one or two days and usually followed increased activity, stress situations, or infections. Minor, self-limiting flare-ups occurred just before the menses in about one half of the menstruant women.

Variation in maximum response. There was wide variation in response to therapy. About 25 per cent of the patients obtained complete relief of joint manifestations within a few months after the onset of therapy, while in 37 per cent the same degree of improvement did not appear for from six to 12 months. In 38 per cent of the patients some improvement occurred, but remained incomplete; this group was considered to have an insignificant response (grade III or grade IV) (Table 1).

It was observed repeatedly that an initial twofold or threefold increase in dosage of the medication did not hasten the onset of clinical improvement, although the number and the severity of the reactions to the drug were increased.

Response to therapy was unsatisfactory in patients who had relapsed while receiving corticosteroids for prolonged periods of time. It never was possible to substitute either chloroquine phosphate or hydroxychloroquine sulfate for one of the corticosteroids in patients with chronic hypercortisonism without a period of hospitalization and supplementation with other chemotherapeutic agents.[14]

4-Aminoquinoline—Corticosteroid Therapy

Because maximum improvement from therapy with chloroquine phosphate or hydroxychloroquine sulfate usually did not occur before three months of therapy and frequently was delayed longer, prednisone or prednisolone, 3.0 to 7.5 mg. daily, supplemented the 4-aminoquinoline compound during the initial phase of therapy of 187 patients. Limitation of functional capacity usually was the determining factor in deciding whether one of the corticosteroids was to be added to the therapeutic program. Again, it was noted that the stage and the duration of the disease, and the functional capacity of the patient had no direct correlation with response to therapy.

Initial improvement seemed to appear more rapidly when a small dose of a corticosteroid was simultaneously administered with a 4-aminoquinoline com-

pound, but eventual over-all improvement after one year was not significantly better than it was in those patients who received only 4-aminoquinoline compounds. In this group, major improvement occurred in 54 per cent of the patients after the first month of therapy and in 61 per cent after six months. Major improvement (grade I or grade II response) was obtained in 67 per cent of the patients in this group after one year, during which time corticosteroid dosage was reduced by one half or administration of the drug was stopped in 47 per cent. In addition to oral medication, 11 per cent of the patients in this group received initial intraarticular injections during the first three months of therapy because joint swelling had been persistent.[15]

We believe that corticosteroids should be considered only as temporary supplemental adjuncts in the treatment of rheumatoid arthritis. They should be administered in small doses equivalent to from 3 to 7.5 mg. of prednisone per day, and should be reduced or should be stopped as improvement appears. Under no circumstances should they be given without a definite, organized plan for reduction in dosage and for withdrawal. Side effects and complications associated with steroid therapy usually were not apparent when the corticosteroids were administered in this manner. We observed two duodenal and one gastric ulcer in three patients who were receiving 3 mg. of prednisone or less per day for periods ranging between 16 and 21 months. The incidence of peptic ulcer in this group was 1.5 per cent (3 of 187 patients). Since none of the patients had symptoms of peptic ulcer prior to the onset of treatment for arthritis, it is likely that the medication was an aggravating factor. No other complications related to steroid therapy were apparent in this group. Patients with diabetes mellitus usually were not given oral steroid therapy.

Combined-Drug Therapy

Of the 487 patients with progressive and persistent disease, 94 patients (40 per cent) were treated with the combination of drugs that we have found to be most effective.[16] This group consisted of 194 patients in whom various forms of therapy had been tried, often with unsatisfactory results. Corticosteroids previously were administered to 133 patients (68 per cent), of which 24 patients (18 per cent) had severe chronic hypercortisonism. Serum polysaccharide-protein ratios[13] were 2.85 or greater. Central nervous system manifestations characteristic of rheumatoid arthritis, including emotional instability, weakness, depression, vasomotor reactions, paresthesias, and altered deep tendon reflexes, were more apparent in this group than in those groups described previously.

The same principles of therapy were instituted as described previously, consisting of the administration of a 4-aminoquinoline compound for long-term maintenance therapy, and a small dose of prednisone or prednisolone from 3.0 to 7.5 mg. daily. In order to suppress inflammation initially, intravenous therapy[17] was administered to all patients and intraarticular injections were given to 76 per cent of the patients in this group.[15] Iproniazid, an inhibitor of monoamine oxidase, was a supplement to the therapeutic program in all

patients of this group. The pharmacologic action, dosage, and rationale for administering this drug have been described.[14,18,19]

Despite greater difficulty in treating these patients because of the administration and adjustment of dosage of several medications, and the need for patient co-operation as well as persistence and patience on the part of the physician, major improvement (grade I or grade II response) eventually occurred in 83 per cent of this group in an irregular and slowly progressive manner.

Side Reactions to Therapy

Drug reactions. Reactions that occur after the use of chloroquine phosphate and hydroxychloroquine sulfate are frequent, but fortunately the majority are transient and insignificant. It is likely that some of the pharmacologic actions responsible for these reactions are also responsible for clinical improvement that occurs in patients with rheumatoid arthritis.

Some type of reaction that involved either the neurovascular system, gastrointestinal tract, skin, or endocrine system occurred in 440 (approximately 55 per cent) of our patients. However, the reactions were transient and disappeared spontaneously in 67 per cent. After the dose of medication was reduced or administration of the drug was temporarily stopped, reactions disappeared in another 26 per cent. Seven per cent of reactions was severe enough to preclude further use of these agents.

In 805 patients who received one of the 4-aminoquinoline compounds there was no evidence of leukopenia, thrombocytopenia, methemoglobinemia, hepatic disease, or psychosis, after treatment was started. In 32 patients (4 per cent) the peripheral leukocyte count was less than 3,000 per cu. mm. before treatment was started. In 21 patients it increased during the period of drug therapy. We believe that the peripheral leukocyte count may fluctuate because of factors related to the disease, rather than because of any serious effect these drugs might have on the bone marrow.

Neurovascular reactions. Of 440 reactions, 49 per cent involved both the nervous and vascular systems; they usually were transient and disappeared spontaneously in 80 per cent of the patients in this group. In all except six of the patients, symptoms subsided when the dosage was reduced temporarily for one or two months. Neurovascular reactions of these patients included: difficulty in visual accommodation, vascular headaches with or without visual aura, vestibular dysfunction, tinnitus, nervousness, insomnia, and mental confusion.

Difficulty in visual accommodation and headaches were the most common reactions in this group. Blurring of vision disappeared within a few weeks and never was a cause for withdrawal of the drug. One third of the patients had throbbing, unilateral headaches. Occasionally a visual aura appeared in patients who never had experienced migraine headaches. Patients susceptible to migraine usually had more frequent and more severe headaches during the first few months of therapy. In most instances the headaches subsided spontaneously within a few weeks after the onset of therapy.

Vestibular dysfunction was manifested by a sensation of imbalance or of light-headedness, but usually not by a true vertigo. Symptoms occurred when the head was turned quickly, and persisted for only a few seconds. Usually this reaction subsided spontaneously within a few weeks without reduction in dosage of medication.

Tinnitus occurred in 11 patients and disappeared spontaneously in eight while medication was continued without reduction in dosage. In three patients, tinnitus disappeared when the dose of medication was reduced. In no patient did it persist beyond a few weeks.

Insomnia and increased nervousness, which occurred in 13 patients of this group, were controlled with sedation. One 58-year-old woman experienced temporary mental confusion that lasted about 36 hours after medication was started; it subsided spontaneously while medication was continued.

Gastrointestinal reactions. Of 805 patients, 17 per cent had gastrointestinal reactions that included: nausea, anorexia, vomiting, bloating, abdominal cramps, heartburn, diarrhea, and loss in weight. Thirty-one per cent of all reactions involved the gastrointestinal tract. They were of greater significance than the neurovascular reactions because they were not so well tolerated and in some instances they did not subside spontaneously, especially when larger doses of the drugs were administered initially.

There was a significant difference between the incidence of gastrointestinal reactions related to hydroxychloroquine sulfate (11 per cent) and those related to chloroquine phosphate (19 per cent). In 60 per cent of the patients who had gastrointestinal reactions, nausea and anorexia occurred soon after medication was started. The most serious gastrointestinal reactions were: anorexia with loss in weight (41 patients), diarrhea (11 patients), and persistent vomiting (4 patients). In the group of 106 patients receiving one of the 4-aminoquinoline compounds as the sole therapeutic agent, only one patient had a duodenal ulcer.

Dermatologic reactions. Skin reactions from chloroquine phosphate and from hydroxychloroquine sulfate were about equally frequent. These were the most distressing as well as the most serious of all of the drug reactions. The skin lesions varied greatly in character and extent and accounted for 12 per cent of all drug reactions; about one half of these were considered serious.

The types of skin reactions included: dryness of the skin, itching, urticaria, morbilliform eruptions, maculopapular eruptions, desquamating lesions, exfoliating lesions, increased pigmentation, alopecia, and graying or bleaching of the hair. Pre-existing psoriatic lesions and those involved with necrotizing arteritis were susceptible to exacerbations. In 76 per cent of the patients in whom there was a skin reaction other than increased pigmentation, alopecia, or color changes of the hair, the reaction appeared within the first month of treatment. The less serious skin reactions consisted of dryness, itching and urticarial reactions. Maculopapular or morbilliform eruptions usually were followed by generalized desquamation that began over the face and shoulders and slowly spread down over the upper extremities, the trunk, and finally the lower extremities. The entire reaction evolved in from five days to two weeks. When the

reaction was mild, the medication was stopped and one of the antihistaminic agents was administered. For more severe reactions, prednisone was administered in doses of 5 mg. three times daily and, more recently, triamcinolone* (2 to 4 mg. three times daily) has been a more effective agent in hastening the reversal of the skin reactions.

Patients with psoriasis appeared to be more susceptible to severe skin reactions than were other patients. We have treated 23 patients with psoriasis and rheumatoid arthritis, 16 of whom improved satisfactorily with disappearance or some lessening of the skin lesions. Severe maculopapular eruptions appeared in five patients, two of whom later had generalized exfoliating lesions that persisted for weeks after the 4-aminoquinoline therapy had been discontinued. One of these patients had a severe exacerbation of psoriasis one week after the exfoliating lesions disappeared. The psoriasis at that time was more severe than it had ever been and was unaffected by the administration of prednisone in doses of 5 mg. four times daily. Triamcinolone was administered (4 mg. three times daily), which resulted in partial improvement of the psoriatic skin lesions. Another patient with psoriasis and arthritis had improvement in joint manifestations but not in skin lesions while receiving chloroquine phosphate. He was admitted to the hospital for Goeckerman (tar and ultraviolet) treatment, but failed to respond until chloroquine phosphate therapy was stopped. A patient with severe psoriasis and mild rheumatoid arthritis was given 250 mg. of chloroquine phosphate daily. After two weeks an extensive urticarial reaction occurred and an exacerbation of the psoriasis, which responded slowly and incompletely to triamcinolone.

Bleaching or graying of the hair occurred in four patients. Chloroquine phosphate was administered to three of these patients in excessive amounts varying between 750 mg. and 2.0 gm. per day for three months or longer. The fourth patient received 600 mg. of hydroxychloroquine sulfate daily for two months, when the hair began to lighten in color. Goldman and Preston[20] reported one case in which bleaching of the hair was followed by the return to the normal color despite continuance of the drug.

Four women had partial alopecia while they were receiving one of the 4-aminoquinoline compounds. Patches of alopecia appeared in two patients who were receiving hydroxychloroquine sulfate in doses of 600 mg. daily for three and six months respectively. In another patient mild alopecia occurred at the onset of her arthritis, subsided during treatment with chloroquine phosphate, 250 mg. daily, and returned six months later while she was still receiving therapy. In the fourth patient, after eight months of 250 mg. daily of chloroquine phosphate, alopecia and graying of the hair developed simultaneously; both conditions subsided when the medication was stopped.

Excessive pigmentation of the exposed areas of the skin occurred routinely in most patients during the summer with the use of either drug. It disappeared slowly and incompletely during the winter (Fig. 1).

Aristocort was supplied through the courtesy of Lederle Laboratories Division, American Cyanamid Company, Pearl River, New York.

Fig. 1. Photo showing excessive pigmentation on hand and forearm exposed to sunlight.

Endocrine dysfunction. During therapy, alteration in menstrual periods occurred in 11 per cent of menstruant women. Usually these patients had intermenstrual spotting or excessive menstrual flow. Dilatation and curettage was performed in six patients. Microscopic study of endometrial tissue disclosed hypertrophic endometrium.

Theories of Pharmacologic Action

The mechanism of pharmacologic action of the 4-aminoquinoline compounds responsible for clinical improvement in patients with active rheumatoid arthritis is not known. The pharmacologic adage that "no drug has a single action" should be emphasized, as it is likely that these 4-aminoquinoline compounds have a wide spectrum of stimulating and inhibiting actions, both in the central nervous system and in the peripheral tissues.

Previously we postulated that two major biochemic alterations might be related to the disease manifestations characteristic of rheumatoid arthritis.[14] A central nervous system defect manifested by decreased neurohormonal activity was suggested as a factor responsible for nonarticular manifestations, including generalized weakness, emotional instability, depression, fatigability, autonomic imbalance, paresthesias, vasomotor reactions, some instances of muscle atrophy, and altered tendon reflexes.

We have reported that the nonarticular manifestations are alleviated by the administration of iproniazid, an inhibitor of monoamine oxidase.[14] Brodie and Shore[21] have postulated that serotonin, rather than acetylcholine, is the chemical transmitter of nerve impulses in the central parasympathetic system, and that norepinephrine is the chemical transmitter in the central sympathetic system. If this concept is correct, we can assume that improvement in central nervous system manifestations following the administration of iproniazid may result from delayed inactivation of certain neurohormones, namely serotonin and norepinephrine.

Inhibition of cholinesterase in plasma, and in erythrocytes, resulting from the administration of chloroquine phosphate has been reported.[22] It is likely that inhibition of cholinesterase would result in delayed destruction of acetylcholine, thus further enhancing the transmission of nerve impulses through cholinergic nerve fibers. However, the initial improvement that occurs in central nervous system manifestations after the administration of 4-aminoquinoline compounds is less significant than that after iproniazid.

Neither chloroquine phosphate nor hydroxychloroquine sulfate are potent inhibitors of amine oxidase, inasmuch as their inhibitory effect on amine oxidase activity of isolated mitochondria of rat liver is approximately two hundredths as active as that of iproniazid.[23] It is entirely possible that, although the mechanism of action is different, increased neurohormonal activity occurs from the administration both of iproniazid and of chloroquine phosphate or hydroxychloroquine sulfate.

Decreased cholinesterase has been reported[24] as occurring during pregnancy, but it is not known whether a relationship exists between the low cholinesterase and the spontaneous improvement that frequently occurs in pregnant women who have rheumatoid arthritis. It is interesting that neurologic manifestations occurred in a woman who, in the fifth month of pregnancy, accidentally took an overdose of chloroquine phosphate (from 1.5 to 3.5 gm.).[25] One hour later she experienced double vision and severe nausea, and suddenly fainted. Other symptoms included vomiting, depressed respiration, difficulty in swallowing, paresthesia, and anesthesia. She recovered completely within 36 hours with no adverse effect on the pregnancy.[25] Perhaps those symptoms resulted from inhibition of cholinesterase that already was depressed as a result of pregnancy.

Decreased cholinesterase has been noted in normal persons,[26] and the theoretical possibility that persons with pre-existing low concentrations are more susceptible to certain drug reactions that accompany the administration of 4-aminoquinoline compounds is under investigation.

In addition to a biochemic alteration within the central nervous system, we have postulated a peripheral biochemic defect within the mesenchymal tissues manifested by increased activity of tissue catecholamines and increased formation of mucopolysaccharides in patients with active rheumatoid arthritis.

We are investigating the possibility that increased activity of certain catecholamines or other irritating substances may cause both proliferation of fibrous tissue and the inflammatory reaction characteristic of rheumatoid arthritis. We have reported elsewhere[19] that either free serotonin or histamine in minute

amounts is capable of producing an acute inflammatory reaction when injected into noninvolved joint tissue of patients with active rheumatoid arthritis; this reaction is less severe in nonrheumatoid persons.

The possibility of a cause-and-effect relationship between serotonin and the proliferation of fibrous tissue needs further investigation before significance can be attached to the numerous descriptions of fibrotic right-sided valvular cardiac lesions and masses of fibrous tissue surrounding pelvic organs and lower abdominal arteries in patients with metastatic carcinoid tumors associated with increased concentration of serotonin in the blood. Although we have observed normal concentrations of serotonin in the blood of patients who have active rheumatoid arthritis, this does not imply that a biochemic alteration within the tissues may not exist.

Many investigators are of the opinion that the mast cell is an important functional component of connective tissue. It is well known that mast cells are rich in polysaccharides and histamine.[27] Recently, on direct analysis, mast cells isolated from rat peritoneum contained serotonin.[28] Histamine liberation has been reported after the administration of chloroquine phosphate in the rat.[29] In many instances histamine liberators are capable of damaging mast cells. However, it must be emphasized that the liberation of histamine does not necessarily imply that is was released from mast cells and, perhaps most important, it is well known that since there is marked species difference in pharmacologic response, a reaction that occurs in the rat cannot be assumed to occur in the human. We are currently investigating the possibility that 4-aminoquinoline compounds are antimetabolites that decrease activity of mast cells in patients with active rheumatoid arthritis.

Clinically the 4-aminoquinoline compounds seem to affect primarily the peripheral or mesenchymal manifestations of the disease, and secondarily the central nervous system manifestations, in contrast to iproniazid, which affects primarily the nonarticular or clinical features related to the central nervous system, and has little effect peripherally on mesenchymal tissue in the small dosages that we use.

Discussion

It is well known that rheumatoid arthritis is a complicated disease, of unknown etiology, which involves many systems of the body, and that no specific therapy is available. Consequently, current treatment is directed toward control of the numerous disease manifestations which vary greatly.

There is complete agreement among investigators that no single agent is capable of controlling all disease manifestations indefinitely without relapse or drug reactions. The desirable and undesirable features of the 4-aminoquinoline compounds are becoming apparent, although we believe that more experience and time are necessary before final conclusions can be made as to their true value as therapeutic agents for rheumatoid arthritis and related diseases.

Desirable features. An important desirable feature of these compounds is the low incidence of *serious* drug reactions during long-term maintenance therapy. It should be kept in mind that certain drug reactions occur frequently and are of temporary duration; therefore, administration of the drug need not be stopped. All drug reactions that were considered serious were completely reversible when the drug therapy was discontinued.

There is a low incidence in major relapse after the attainment of maximum improvement. However, minor fluctuations manifested by transient aching, stiffness or mild joint swelling, frequently follow physical overactivity and emotional stress.

The 4-aminoquinoline compounds can be administered orally and simultaneously with other therapeutic agents[14,16] to patients whose response to therapy previously has been unsatisfactory and, after improvement occurs, the use of therapeutic agents other than the 4-aminoquinoline compound can be stopped.

There are no apparent contraindications to the use of these compounds in cases of pregnancy, peptic ulcer, pulmonary tuberculosis, diabetes mellitus, or hypertension.

Undesirable features. One of the most undesirable features of the 4-aminoquinoline compounds is that the patient responds slowly to therapy, and maximum improvement may be delayed for from six months to one year.

In about one third of the patients there are joint manifestations that do not subside completely, and the central nervous system manifestations characteristic of rheumatoid arthritis initially are not significantly improved with the administration of these drugs.

Cystic changes and demineralization of bone may develop in spite of the disappearance of joint pain and swelling during chloroquine therapy. A 16-year-old girl had rheumatoid arthritis with involvement of both wrists and knees. The joints were moderately swollen and painful on motion. Six months after the onset of joint manifestations, chloroquine phosphate (250 mg. daily) was started. Roentgenograms of the joints taken before medication was started revealed normal structure. Although joint swelling and tenderness disappeared after three months of therapy, medication was continued. One year after the onset of therapy, roentgenograms showed a generalized demineralization of the bones in the hand and the wrist and a cystic change in the navicular bone (Fig. 2).

The most serious reactions involve the skin, and patients with psoriasis are highly susceptible to a variety of skin reactions, including an exacerbation of their psoriatic lesions. We believe that it is best to avoid the use of these compounds when psoriasis is present.

The use of 4-aminoquinoline compounds in rheumatoid arthritis. In patients with rheumatoid arthritis the clinical response to 4-aminoquinoline compounds in many ways resembles that of patients with chronic gouty arthritis who are treated solely with probenecid. In each disease there usually is a delay in clinical improvement. If the dosage of medication is increased, there is little or no significant immediate effect on the course of either disease, except occasionally

when transient exacerbations appear shortly after the onset of therapy. After periods from six months to one year, patients with chronic gouty arthritis are less susceptible to acute exacerbations, but mild flare-ups still may occur. This also is characteristic of most patients with rheumatoid arthritis treated with one of the 4-aminoquinoline compounds. In both diseases, long-term administration of these drugs usually results in maintenance of clinical improvement.

A B

Fig. 2. (A) Roentgenogram taken before the patient was given chloroquine phosphate therapy. (B) One year after beginning chloroquine phosphate therapy; note generalized demineralization of the bones in the hand and the wrist, and a cystic change in the navicular bone.

Combined-drug therapy has been advocated and used with increased effectiveness in chronic gouty arthritis. Acute exacerbations are treated separately with drugs that quickly suppress the acute attack, while probenecid is given to maintain the improved state and to prevent future exacerbations. Because of the characteristic response to 4-aminoquinoline compounds we have applied the same principle of therapy to patients with progressive and persistently active rheumatoid arthritis. One of the 4-aminoquinoline compounds is administered primarily to maintain long-term suppression of connective-tissue inflammation. Small doses of oral corticosteroids and/or intravenous corticotropin with or without nitrogen mustard may be used temporarily at the onset of therapy to suppress inflammation rapidly. During the first few months of therapy, central nervous system manifestations are treated with iproniazid. Thus, an individualized program of therapy can be instituted for each patient depending upon the disease manifestations present at the time treatment is started. As improvement

occurs, the drugs can be withdrawn in orderly fashion, and maintenance therapy can be continued with a 4-aminoquinoline compound.

Summary

1. Chloroquine phosphate or hydroxychloroquine sulfate was administered to 805 patients with rheumatoid arthritis and allied diseases for periods ranging up to three years.

2. Of 106 patients with rheumatoid arthritis who were given only a 4-aminoquinoline drug, there was major improvement in 62 per cent. There was a wide variation in response: less than 25 per cent of patients obtained major improvement within the first three months; 37 per cent obtained similar improvement after 12 months; 38 per cent showed an insignificant response after 18 months.

3. Reactions related to the administration of 4-aminoquinoline compounds in 805 patients are grouped as neurovascular, gastrointestinal, dermatologic, and endocrine. Although 55 per cent of patients exhibited some reaction to the drugs, 67 per cent of these reactions cleared spontaneously while medication was continued. Seven per cent of toxic reactions was serious enough to require withdrawal of the 4-aminoquinoline compound.

4. The pharmacologic action of these compounds is not known, although biochemic alterations occur within the central nervous system and peripheral tissues.

5. The desirable features of therapy using 4-aminoquinoline compounds are the low incidence of serious drug reactions and of chronic toxicity, the ease of administration, the compatibility with other therapeutic agents, and the low incidence of relapse after maximum improvement has been obtained.

6. The undesirable features of 4-aminoquinoline compounds are the delayed onset of major improvement, the persistence of minor disease fluctuations and the lack of major improvement that is observed in one third or more of the patients, and sometimes an apparent susceptibility to skin reactions that may be serious although not necessarily frequent.

7. Those patients in whom slow onset in clinical improvement or incomplete response to therapy was anticipated, were given supplemental agents to induce further suppression of the disease. The 4-aminoquinoline drugs together with supplemental agents administered in nontoxic doses effectively maintained suppression of the disease in 83 per cent of 194 patients followed for 18 months. Emphasis is placed on a definite, orderly withdrawal of supplemental agents as improvement occurs.

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HEMATOLOGIC CHANGES OBSERVED AFTER EXTRACORPOREAL CIRCULATION DURING OPEN-HEART OPERATIONS*

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HEMATOLOGIC studies were performed to detect whether or not alterations occurred in the formed elements of the blood in 12 consecutive patients who underwent open-heart operations with the use of heart-lung machines. The rotating disk types of oxygenator were used, the Björk, the Kay and Cross, and the Melrose. Eight of the patients were children less than 14 years of age, and four were adults. The duration of the extracorporeal circulation ranged from 9 to 24 minutes and averaged 18 minutes.

Methods and Technic

The following hematologic determinations were made prior to operation and usually repeated on the first, third, and seventh postoperative days: hemoglobin content of the blood, erythrocyte and leukocyte counts, differential leukocyte count, hematocrit value, icterus index, reticulocyte percentage, platelet count (Rees-Ecker method), bleeding time (Ivy method), coagulation time (Lee-White method), clot retraction, and one-stage prothrombin time. Additional determinations, such as plasma hemoglobin, fibrinogen, fibrinolytic activity, serum bilirubin value, Coombs reaction, and protamine titration, were made when indicated. For several patients, hematologic determinations were made periodically for six months after operation.

Analysis of Results

A review of the data indicates that no serious hematologic changes occurred in the 12 patients whose circulation was maintained by the oxygenator during open-heart operations.

The clinical examinations and the laboratory studies disclosed no hematologic disorders prior to operation. Three patients had a moderate, and one patient, a severe, hypoxemic erythrocytosis (hematocrit value of 72 ml. per 100 ml. of blood) which disappeared after surgical correction of the congenital cardiac defect. During extracorporeal circulation all of the patients received sufficient heparin to increase the blood coagulation time to several hours.

The significant findings are summarized according to three categories: (1) anemia and hemolysis, (2) leukocytic changes, and (3) hemorrhagic studies.

**Open-heart operations were performed by the open-heart team: Donald B. Effler, M.D., Department of Thoracic Surgery, and Willem J. Kolff, M.D., Department of Artificial Organs.*

(*1*) *Anemia and hemolysis.* In eight patients a mild or moderate decrease of erythrocytes, hemoglobin, and hematocrit value occurred within the week after operation. The anemia was normocytic and normochromic in type. Study of the Wright-stained blood films revealed no cytologic abnormalities of the erythrocytes. Spherocytic red blood cells and "target" cells were not observed. In nine patients the hematocrit values decreased no more than 5 volumes per cent below the preoperative values. In one patient the hematocrit value decreased from 42 cc. to 30 cc. because of hemorrhage. In two patients the erythroid elements were slightly increased.

Evidence of marked hemolysis was not observed in any of the 12 patients. There was no visible hemoglobinemia or hemoglobinuria. The plasma hemoglobin value was not quantitatively determined in all patients. In two of the patients the plasma hemoglobin values were 91 mg. per 100 ml., and 101 mg. per 100 ml., respectively, during the period of extracorporeal circulation.

Jaundice was evident in one patient in whom there was bleeding into the pericardial space which produced cardiac tamponade requiring reoperation. In that patient the icterus index was 25 units, indirect serum bilirubin was 2.8 mg. per 100 ml., and the reticulocyte count was 2.7 per cent. These findings suggest that the jaundice was the result of absorption of blood pigments from the pericardial space and was not due to excessive intravascular hemolysis. The icterus index was elevated to 13 and to 18 units, respectively, in two patients during the postoperative period. In the other nine patients the icterus index was unchanged.

A mild reticulocytosis occurred in eight patients during the first week after operation; the highest value recorded was 10 per cent. The data suggest that the marrow had responded to a mild postoperative anemia. The osmotic fragility of the erythrocytes was found to be normal in four of the patients.

The hematologic findings, however, do not exclude the presence of some increased hemolysis as a result of trauma of the erythrocytes by the oxygenator.

(*2*) *Leukocytic changes.* The leukocyte count increased to moderate values in 10 of the patients, the highest count being 23,500 per cu. mm., and several ranging between 15,000 and 20,000 per cu. mm. The leukocytosis was due to an increase of neutrophilic granulocytes. A shift to the left was usually observed. One patient had a transitory neutropenia. No cytologic abnormalities of the granulocytic cells were observed on the stained blood films. There was no significant quantitative change in the eosinophils. The monocytic cells in two patients contained conspicuous cytoplasmic vacuoles during extracorporeal circulation.

There were no significant quantitative changes in the lymphocytes, but in five patients (four children and one adult) "atypical" or prolymphocytes were conspicuous. The number of prolymphocytes ranged between 5 and 10 per cent of the differential leukocyte count; they appeared to be similar to those observed in patients with infectious mononucleosis. In one child these cells reached a peak of 22 per cent of the leukocyte count and persisted for three months. There was no clinical evidence of infectious mononucleosis and the heterophil agglutination titer was 1:8.

(*3*) *Hemorrhagic studies.* The platelet count was slightly decreased in four of the patients during the first three days after operation, but without clinical evidence of excessive bleeding. The lowest platelet count was 100,000 per cu. mm. No significant qualitative changes of the platelets were observed on the stained blood films. In the other eight patients no depression of the platelet count occurred. There was no significant abnormality of clot retraction in this series of patients.

The coagulation time 24 hours after operation was slightly prolonged in two of the patients. The coagulation time was 22 minutes in one patient and 24 minutes in another, compared to the normal range of from 10 to 20 minutes. The patient whose coagulation time was 24 minutes had a large pericardial hemorrhage that was thought to be due primarily to a technical failure rather than to a defect in the clotting mechanism.

Recently, in 10 additional patients there has been no prolongation of the coagulation time on determinations performed four hours after the completion of the open-heart operations. Moreover, in each case the retraction of the clot was adequate. In our series of 12 patients reported here, the one-stage prothrombin time was slightly prolonged in five patients in the seven-day postoperative period. The values ranged from 15 to 18 seconds, as compared to the normal value of 14 seconds. The longest prothrombin time observed was 21 seconds and occurred 24 hours after operation in the patient previously described who had pericardial hemorrhage. This was the only patient in the 12 of this group in whom coronary sinus blood sucked from the open heart was reintroduced into the circulation.

There was evidence of slight transitory fibrinolysis in two of the patients. There was no significant change in the fibrinogen value of any of the patients.

Comment

One child in our group of 12 patients died after a second open-heart operation. The other patients survived, and follow-up hematologic studies on four of these, for periods as long as eight months, revealed no significant change except the presence of "atypical" lymphocytes. The observations for this small group of patients suggests that no serious disturbances of the formed elements of the blood occur after the use of the rotating disk type of oxygenators for extracorporeal circulation.

Summary

Hematologic studies in 12 consecutive patients who underwent open-heart operations with extracorporeal circulation disclosed the following changes in the postoperative period: (1) mild anemia, (2) minimal hemolysis of erythrocytes, (3) leukocytosis, (4) "atypical" lymphocytes, (5) slight reticulocytosis,

and (6) minimal prolongation of the prothrombin time. No major manifestations of hemolytic anemia or hemorrhagic diatheses were observed.

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++*Harvard Medical School, Boston, Massachusetts.*

†*American Heart Association; and Medical Research Institute, Michael Reese Hospital, Chicago, Illinois.*

THE FRANK E. BUNTS EDUCATIONAL INSTITUTE

affiliated with

THE CLEVELAND CLINIC FOUNDATION

announces a postgraduate course in clinical pathology

sponsored by the Cleveland Society of Pathologists

on May 15 and 16, 1958

The course is open to all physicians but is directed primarily to the needs and interests of pathologists. It is hoped that bacteriologists and chemists with Ph.D. degrees, and other qualified persons, will be interested in attending the course.

The lectures will be given in the auditorium on the fourth floor of the North Clinic Building located at Euclid Avenue and East 93rd Street. Nearby hotels having comfortable accommodations are the Bolton Square, Fenway Hall, Park Lane Villa, Tudor Arms, and Wade Park Manor. The University Center Motel is across the street from the Cleveland Clinic.

This course has been co-ordinated with and immediately precedes the spring meeting of the Ohio Society of Pathologists, which will be held Saturday, May 17, 1958.

Tentative Program

Thursday, May 15, 1958

Morning Session — ADRIAN HAINLINE, JR., Ph.D., *Presiding*

8:30- 9:00	.	Registration
9:00- 9:15	.	Introductory Remarks and Welcome . . . CHARLES L. LEEDHAM, M.D.
9:15- 9:35	.	TRI^{131} Uptake in Thyroid Disease . . . . JOHN W. KING, M.D., Ph.D.
9:35- 9:55	.	Blood-Volume Determinations . . . . . CARL E. WASMUTH, M.D.
9:55-10:50	.	Medical Aspects of Biophysics . SERAFEIM P. MASOUREDIS, M.D., Ph.D.*
10:50-11:05	.	Intermission
11:05-11:25	.	Abnormal Hemoglobins . . . . . LENA A. LEWIS, Ph.D.
11:25-11:45	.	Certain Aspects of Fungous Disease . LAWRENCE J. MCCORMACK, M.D.
11:45-12:05	.	Determination of Barbiturate Intoxication . . IRVING SUNSHINE, Ph.D.*
12:05-12:30	.	Questions and Answers
12-30-	.	Luncheon—*Courtesy of Bunts Institute*

Afternoon Session — JOHN W. KING, M.D., Ph.D., *Presiding*

2:00- 2:20	.	Hemophilia . . . . . MARY C. HARMON, M.D.
2:20- 2:40	.	Parahemophilia . . . . . JAMES S. HEWLETT, M.D.

*Guest speaker.

2:40- 3:00 . The Antihuman-Globulin (Coombs) Test . GEORGE C. HOFFMAN, M.D.
3:00- 3:50 . Clinical and Experimental Transfusion Reactions . . . . . SCOTT N. SWISHER, M.D.*
3:50- 4:10 . Intermission
4:10- 4:30 . ABO Sensitizations . . . . . DONALD A. SENHAUSER, M.D.
4:30- 4:50 . Laboratory Technics in Lupus Erythematosus. JOHN R. HASERICK, M.D.
4:50- 5:00 . Questions and Answers
5:30- 7:00 . Hospitality Hour—Wade Park Manor

Friday, May 16, 1958

Morning Session LAWRENCE J. MCCORMACK, M.D., *Presiding*

9:00- 9:20 . The Addis Count . . . . . HARRIET P. DUSTAN, M.D.
9:20- 9:40 . Blood pH Measurement . . . . . WILLARD R. FAULKNER, Ph.D.
9:40-10:00 . Protein-Bound Iodine Determination . . . . DEVINA C. TWEED, Ph.D.
10:00-10:50 . The Use of Isotopes in Clinical Laboratory Diagnosis . . . . . SERAFEIM P. MASOUREDIS, M.D., Ph.D.*
10:50-11:05 . Intermission
11:05-11:25 . Latex Fixation Tests in Rheumatic Diseases . . . . . ARTHUR L. SCHERBEL, M.D.
11:25-11:45 . Technics of Urine Culture . . . . . JOHN W. KING, M.D., Ph.D.
11:45-12:05 . Asian Influenza . . . . . ROBERT O. OSEASOHN, M.D.*
12:05-12:30 . Questions and Answers
12:30- . Luncheon—*Courtesy of Bunts Institute*

Afternoon Session JOHN W. KING, M.D., Ph.D., *Presiding*

2:00- 2:20 . Laboratory Diagnosis of Tuberculosis . . . . VICTOR S. HIRSCH, M.D.*
2:20- 2:40 . Serum Iron Determination . . . . . ADRIAN HAINLINE, JR., Ph.D.
2:40- 3:30 . Acquired Hemolytic Anemia with Special Reference to Red Cell Physiology . . . . . SCOTT N. SWISHER, M.D.*
3:30- 3:45 . Intermission
3:45- 4:05 . Blood Platelets . . . . . WILLIAM A. HAWK, M.D.
4:05- 4:25 . Automation in the Laboratory . . . . . LEONARD T. SKEGGS, Ph.D.*
4:25- 5:00 . Questions, Answers, and Critique

Affiliations of Guest Speakers

VICTOR S. HIRSCH, M.D., Visiting Pathologist, Sunny Acres Hospital, Cleveland, Ohio.

SERAFEIM P. MASOUREDIS, M.D., Ph.D., Associate Professor of Pathology, University of Pittsburgh, School of Medicine; Associate Director, Central Blood Bank, Pittsburgh, Pennsylvania.

ROBERT O. OSEASOHN, M.D., Department of Medicine and Preventive Medicine, School of Medicine of Western Reserve University, and University Hospitals, Cleveland, Ohio.

LEONARD T. SKEGGS, Ph.D., Biochemist, Crile Veterans Administration Hospital, Cleveland, Ohio.

IRVING SUNSHINE, Ph.D., Toxicologist, Cuyahoga County Coroner's Office; Assistant Professor of Toxicology, School of Medicine of Western Reserve University, Cleveland, Ohio.

SCOTT N. SWISHER, M.D., Associate Professor of Medicine, University of Rochester, School of Medicine and Dentistry, Rochester, New York.

**Guest Speaker.*

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